INTERNATIONAL RECORD OF MEDICINE

GENERAL PRACTICE CLINICS

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL RECORD, FOUNDED PHILADELPHIA, 1857

VOL. 167 NO. 4 APRIL 1954

INTERNATIONAL RECORD OF MEDICINE

SKETCH FOR A UNIFIED THEORY OF MEDICINE — *Hans Selye*

DR. WINFRED OVERHOLSER HONORED WITH AWARD

DR. HENRY WELCH CITED FOR DISTINGUISHED SERVICE

MEDICAL HUMANITIES

THE ARTIST AS PHYSICIAN
(MEDICAL PHILOSOPHY IN THE RENAISSANCE) — *Félix Martí-Ibáñez*

GENERAL PRACTICE CLINICS

ADVANCE REPORTS AND HIGHLIGHTS FROM CURRENT MEDICAL MEETINGS

ABSTRACTS OF PAPERS DELIVERED BEFORE THE

Junior Faculty and Staff, Women's Medical College of Pennsylvania: Albert Einstein Medical Center, Southern Division, Philadelphia: Medical Research Forum, N. Y. Academy of Medicine; Royal Society of Medicine, Section of Endocrinology, London; Philadelphia County Medical Society, Scientific Meeting.

A JOURNAL OF MD PUBLICATIONS, INC.

EMOTIONAL SYMPTOMS

IN 50% of menstruating women,[1] emotional symptoms have a *physical* basis that you can treat *medically*. The syndrome of premenstrual tension—depression, irritability, anxiety, headaches, fatigue, mastalgia, edema—"cannot be dismissed as being neurotic or primarily phychogenic."[2]

Effective in 80-90% of cases, reports Morton:[3,4] "The greatest improvement was noted in the nervous and mental symptoms."[3]

1. Freed, S. C., Internat. Rec. Med. 166:465 (Nov.) 1953.
2. Rees, L., J. Ment. Sc. 99:62 (Jan.) 1953. 3. Morton, J. H., et al., Am. J. Obst. & Gynec. 65:1182 (June) 1953.
4. Morton, J. H., Internat. Rec. Med. 166:505 (Nov.) 1953.

℞ 2 Pre-mens tablets t.i.d., p.c., for 10 days premenstrually. In bottles of 60. Recommend a high-protein, low-salt diet.

Samples available on request.

PRE-MENS™

FOR THE COMMONEST NERVOUS DISORDER OF WOMEN

Each Pre-mens enteric coated tablet contains:

Ammonium chloride	5.0 gr.
Homatropine methylbromide	0.5 mg.
Caffeine alkaloid	0.5 gr.
Vitamin B_1 (Thiamine HCl)	2.0 mg.
Vitamin B_2 (Riboflavin)	1.0 mg.
Vitamin B_6 (Pyridoxine HCl)	0.5 mg.
Calcium pantothenate	1.0 mg.
Niacinamide	5.0 mg.

The Purdue Frederick Company

New York 14, New York

International

RECORD OF MEDICINE

A Journal of Advanced Experimental and Clinical Reports

and

GENERAL PRACTICE CLINICS

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

VOL. 167 NO. 4 • WHOLE NUMBER 2854 • APRIL 1954

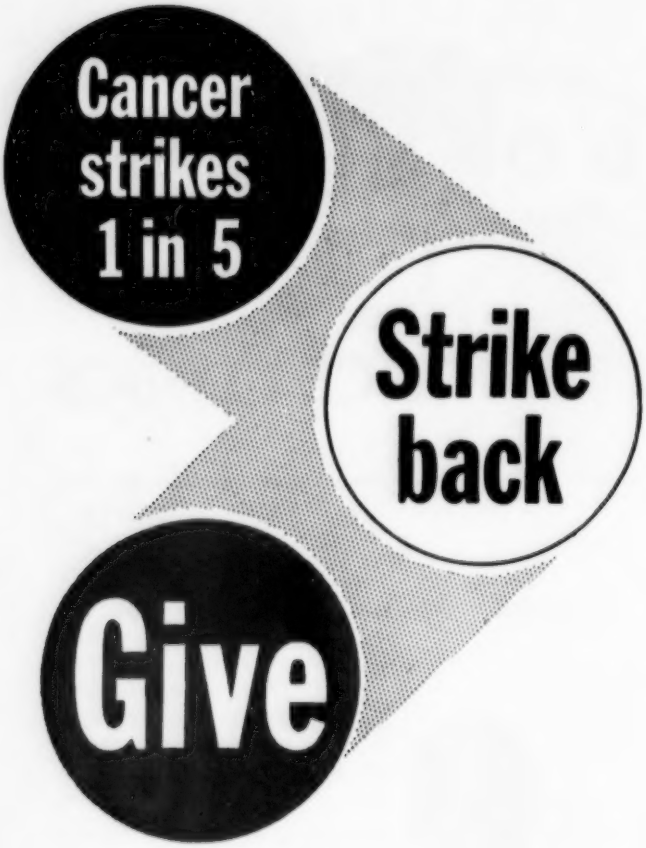
Published Monthly by

MD PUBLICATIONS, Inc.

Félix Martí-Ibáñez, M.D., *President*

Editorial and Advertising Offices	*Circulation Offices*	
30 East 60th Street New York 22, N. Y.	910 17th St., N.W. Washington, D. C.	30 East 60th Street New York 22, N. Y.

A cumulative cross reference index is included in the final issue of each volume. Subscription rate: 1 year, $11.00, 3 years, $28.00. Copyright 1954 by MD Publications, Inc. Entered as second class matter at Washington, D. C. under the Act of March 3, 1879. Printed in U. S. A.



Your gifts to the American Cancer Society help guard those you love.

Your dollars support research in a hundred laboratories and universities . . . spread life-saving information . . . ease pain and suffering . . . provide facilities for treatment and care of cancer patients.

It is a sobering fact that cancer may strike anyone tomorrow: strike back today with a gift to the American Cancer Society. You may mail it, simply addressed **CANCER**, c/o your local post office.

American Cancer Society

EDITORIAL BOARD

Félix Martí-Ibáñez, M.D., *International Editor*

National

Fred L. Adair, M.D., *University of Chicago*
Harry L. Arnold, Jr., M.D., *Editor, Hawaii Medical Journal, Honolulu, Hawaii*
W. Wayne Babcock, M.D., *Temple University*
Howard C. Ballenger, M.D., *Northwestern University*
Conrad Berens, M.D., *The Ophthalmological Foundation*
Alexander W. Blain, M.D., *Wayne University*
Alfred Blalock, M.D., *Johns Hopkins University*
W. F. Braasch, M.D., *Mayo Clinic*
J. Mackenzie Brown, M.D., *University of Southern California*
Morton S. Bryer, M.D., *The Mount Sinai Hospital*
Leroy A. Calkins, M.D., *University of Kansas*
Bayard Carter, M.D., *Duke University*
Russel L. Cecil, M.D., *Cornell University*
Co Tui, M.D., *Creedmoor Institute*
George Morris Coates, M.D., *University of Pennsylvania*
Willard R. Cooke, M.D., *University of Texas*
Frederick A. Coller, M.D., *University of Michigan*
Walter T. Dannreuther, M.D., *New York University*
Clyde L. Deming, M.D., *Yale University School of Medicine*
R. S. Dinsmore, M.D., *Cleveland Clinic*
Henry Dolger, M.D., *New York, N. Y.*
I. E. Drabkin, Ph.D., *The College of the City of New York*
Daniel C. Elkin, M.D., *Emory University*
Ludwig A. Emge, M.D., *Stanford University*
Harold K. Faber, M.D., *Stanford University Hospital*
Harry A. Feldman, M.D., *State University of New York*
Joseph H. Fobes, M.D., *New York Medical College*
A. Stone Freedberg, M.D., *Harvard Medical School, Boston, Mass.*
Willis D. Gatch, M.D., *University of Indiana*
Louis J. Gelber, M.D., *Rockville Center, L. I., N. Y.*
N. C. Gilbert, M.D., *Northwestern University*
David Grob, M.D., *Johns Hopkins Medical School*
Bernard J. Hanley, M.D., *University of Southern California*
French K. Hansel, M.D., *Washington University*
Clyde A. Heatly, M.D., *University of Rochester*
Henry F. Helmholtz, M.D., *Mayo Clinic*
Frank Hinman, M.D., *University of California*
Paul H. Holinger, M.D., *University of Illinois*
Clarence B. Ingraham, M.D., *University of Colorado*
Chevalier L. Jackson, M.D., *Temple University*
J. Bay Jacobs, M.D., *Georgetown University*
Marvin F. Jones, M.D., *New York, N. Y.*
Robert W. Keeton, M.D., *University of Illinois*
Harry H. Kerr, M.D., *George Washington University*
William J. Kerr, M.D., *Blue Lake, California*
I. Newton Kugelmass, M.D., *New York, N. Y.*
Carl H. Lenhart, M.D., *Western Reserve University*
Theodore Lidz, M.D., *Yale University School of Medicine*
Dean M. Lierle, M.D., *University of Iowa*
Ralph H. Major, M.D., *University of Kansas*
Irvine McQuarrie, M.D., *University of Minnesota*
Charles M. Norris, M.D., *Temple University*
Alton Ochsner, M.D., *Tulane University*
Thomas G. Orr, M.D., *University of Kansas*
Henry Boylan Orton, M.D., *New York Polyclinic*
Winfred Overholser, M.D., *George Washington University*
James E. Paullin, M.D., *Emory University*
Franklin L. Payne, M.D., *University of Pennsylvania*
Louis E. Phaneuf, M.D., *Tufts College Med. School*
E. D. Plass, M.D., *University of Iowa*
Tracy J. Putnam, *Beverly Hills, California*
Fred W. Rankin, M.D., *Lexington, Kentucky*
B. O. Raulston, M.D., *University of Southern California*
Lyman G. Richards, M.D., *Harvard University*
Leonard G. Rowntree, M.D., *Miami, Fla.*
Raymond Sackler, M.D., *New York, N. Y.*

MILTON S. SACKS, M.D., *University of Maryland School of Medicine*

MORRIS SCHAEFFER, M.D., *Director, Communicable Disease Center, Montgomery, Ala.*

LEWIS C. SCHEFFEY, M.D., *Jefferson Medical College*

SIDNEY SCHERLIS, M.D., *University of Maryland School of Medicine*

EDWARD A. SCHUMANN, M.D., *Philadelphia, Pa.*

CYRUS C. STURGIS, M.D., *University of Michigan*

HERBERT THOMS, M.D., *Yale University*

DONALD V. TRUEBLOOD, M.D., *Seattle, Wash.*

THEODORE E. WALSH, M.D., *Washington University*

JAMES J. WARING, M.D., *University of Colorado*

KARL M. WILSON, M.D., *University of Rochester*

FRED W. WITTICH, M.D., *Minneapolis, Minn.*

International

ROMA AMYOT, M.D., *Editor-in-Chief, L'Union Medicale du Canada*

GASTON BACHELARD, M.D., *Directeur de l'Institut d'Histoire des Sciences, La Sorbonne, Paris, France*

PAUL DIEPGEN, M.D., *Director of Medizinhistorischen Institutes der Johannes Gutenberg Univ., Mainz, Germany*

PEDRO LAIN ENTRALGO, M.D., *President of the Universidad de Madrid, Madrid, Spain*

PROF. A. GIGON, *Schweizerische Akademie der Medizinischen, Wissenschaften, Basel, Switzerland*

EDV. GOTFREDSEN, M.D., *Director of the Universitetets Medicinsk-Historiske Museum. Copenhagen, Denmark*

DOUGLAS GUTHRIE, M.D., *Professor of the History of Medicine, University of Edinburgh, Edinburgh, Scotland*

WILLY HARTNER, M.D., *Johann Wolfgang Goethe Universität, Frankfurt a. M., Germany*

E. HINTZCHE, M.D., *Anatomisches Institut, Bern, Switzerland*

JUAN B. LASTRES, M.D., *Profesor de Historia de la Medicina, Universidad de San Marcos, Lima, Peru*

ADOLF MEYER-ABICH, M.D., *Hamburg-Blankenese, Elbchaussee 460, Germany*

ANIBAL RUIZ MORENO, M.D., *Profesor de Historia de la Medicina, Buenos Aires, Argentina*

PROF. RODOLFO PÉREZ DE LOS REYES, *Universidad de La Habana, Cuba*

AUGUSTO PI-SUÑER, M.D., *Instituto de Medicina Experimental, Caracas, Venezuela*

ILSE ROSENTHAL-SCHNEIDER, M.D., *The University of Sydney, Sydney, Australia*

KENNETH F. RUSSELL, M.S., F.R.A.C.S., *Associate Professor of Anatomy, The University of Melbourne, Melbourne, Australia*

TH. H. SCHLICHTING, M.D., *Amsterdam, Holland*

PROF. IVOLINO DA VASCONCELLOS, *President, Sociedad Brasileña de Historia da Medicina, Rio de Janeiro, Brazil*

Antibiotics
ANNUAL
1953-1954

Proceedings of the ANTIBIOTIC SYMPOSIUM

Held at the Auditorium, Dept. of Health, Education and Welfare, Oct. 28-30, 1953

Sponsored by

U.S. Dept. of Health, Education, and Welfare, Food and Drug Administration, Division of Antibiotics

In Collaboration with The Journal

Antibiotics and Chemotherapy

Chairman
HENRY WELCH, Ph.D., Director, Division of Antibiotics

Your copy of ANTIBIOTICS ANNUAL 1953-54 entitles you to an up-to-the-minute survey of the latest experimental and clinical research in the antibiotic drug field, including the 102 papers presented by outstanding authorities in the field at this three-day international event in Washington. The timely publication of this 640 page, clothbound volume, affords you the best possible reference to the basic research work on new antibiotic drugs as well as results of laboratory and clinical investigations on presently used antibiotics.

Among the many outstanding contributors to this volume are: Maxwell Finland, M.D., Harvard University; Harry Dowling, M.D., of the University of Illinois; Perrin H. Long, M.D., State University of New York; Ernest Jawetz, M.D., University of California Medical Center; William B. Tucker, M.D., V.A. Hospital, Minneapolis, Minn.; Monroe J. Romansky, M.D., George Washington University School of Medicine; Charles R. Rein, M.D., New York University; Edwin J. Pulaski, M.D., Walter Reed Army Medical Center. Invaluable information is supplied on the new antibiotics tetracycline, dibenzylamine penicillin G, streptogramin, ruticin, hygromycin, puromycin, and methymycin.

You may obtain your copy of this unique volume, which will be a permanent reference book, by filling in the coupon below and returning it to MD Publications Inc., 30 East 60th Street, New York 22, N. Y.

Please send me.....copies of the clothbound ANTIBIOTICS ANNUAL 1953-1954 (Proceedings of the Antibiotics Symposium, October, 1953). Enclosed is my check in the amount of.....($8.00 per copy).

Name .....

Address .....

Bill to .....

Mail this coupon to MD Publications Inc., 30 East 60th Street, New York 22, N. Y.

INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS

INSTRUCTIONS TO CONTRIBUTORS

All manuscripts submitted for publication in INTERNATIONAL RECORD OF MEDICINE should be sent to Doctor Félix Martí-Ibáñez, MD Publications, 30 East 60th St., New York 22, N.Y. Manuscripts should not include data published previously and it is understood that any manuscript submitted is not being submitted elsewhere.

Manuscripts.—All manuscripts should be typewritten, double spaced, and on only one side of paper 8½ by 11 inches. They should be mailed in a flat package. *The original, one carbon copy, and an abstract (approximately 250–300 words) of the article are required.* Original drawings or tracings should not be sent. Glossy photographs, no larger than the manuscript paper, of all illustrations should accompany the copies of the manuscript. Prints should be sufficiently clear to permit the making of engraver's cuts without retouching and to allow reduction to approximately one-third size.

Tables, figures, charts, etc., must be typewritten on separate sheets and should be placed in proper sequence in the manuscript. Footnotes should not be included in the text pages. All references are to be numbered consecutively and typed on a separate sheet. Numerals are used for figures for all definite weights, measurements, percentages, and degrees of temperatures. All indefinite and approximate periods of time and other numerals which are used in a general manner should be spelled out. Standard abbreviations should be used whenever weights and measurements are given in the metric system. The forms to be used are: Gm., ml., Kg., mg., mcg., mm., and l. Per cent should be written out in the text.

Footnotes and Bibliographies should conform to the style of the Quarterly Cumulative Index Medicus published by the American Medical Association. This requires, in the order given, last name of author, initials, title of article in the language in which it was written, name of journal with accepted abbreviation, volume number, page number, and year.

Illustrations.—A reasonable number of half-tone illustrations will be reproduced free of cost to the author but special arrangements must be made with the editor for color plates, elaborate tables, or extra illustrations. Pen drawings and charts should be drawn and lettered only in India ink or black typewriter ribbon (when the typewriter is used). Only good photographic prints or drawings should be supplied for half-tone work. All photographs submitted should be numbered and bear on the back author's name, address, and title of article. Top of picture should be indicated.

Reprints.—Authors will be sent an estimate of the cost of reprints with galley proofs. Reprints may be ordered anytime after manuscript has been set in type but not later than 30 days after the journal has been published.

Business Communications.—All communications in regard to advertising, subscription, change of address, etc., should be addressed to M D Publications, Inc., 30 East 60th Street, New York 22, N. Y. The publisher should be advised of a change in the subscriber's address about 15 days before the date of the issue of the journal with both new and old addresses given.

Subscription Rates.—In the United States and other countries in the United States postal zone—$11.00; single copies, $1.20. In Canada and other foreign countries—$12.00; single copies, $1.40. Remittance for subscriptions should be made by check, draft, post office or express money order, or registered letter payable to M D Publications, Inc.

INTERNATIONAL RECORD OF MEDICINE
and
GENERAL PRACTICE CLINICS

VOL. 167 NO. 4 • WHOLE NUMBER 2854 • APRIL 1954

INTERNATIONAL RECORD OF MEDICINE

The Search for the Philosophical Nature of Disease in the History of Medicine: An Introduction to Hans Selye's "Sketch for a Unified Theory of Medicine" 179

Sketch for a Unified Theory of Medicine 181
Hans Selye

Dr. Winfred Overholser Honored With Award 206

Dr. Henry Welch Cited For Distinguished Service 207

GENERAL PRACTICE CLINICS

Advance Reports from Current Medical Meetings

Certain Aspects of the Problem of Liver Cirrhosis 209
I. Snapper

The Aminoacidurias 213
Maxwell Scarf

Cardiac Pain in Man: Blocking Effect of Ethyl Chloride Spray on the Angina of Ergonovine 216
Isidore Stein, Seymour H. Rinzler, Hyman Bakst, Joseph Weinstein, Robert Gittler, and Janet Travell

Practical Application of Endocrinology to Other Branches of Medicine: Illustrated by a Case of Male Hypogonadism 217
Raymond Greene

Familial Hypogonadism 218
D. G. Ferriman

Furadantin in the Treatment of Infections Due to Antibiotic Resistant Organisms 218
Charles E. Friedgood and Charles B. Ripstein

Hearing Problems: Their Detection and Management 220
David Myers

MEDICAL HUMANITIES

The Artist as Physician (Medical Philosophy in the Renaissance) 221
Félix Martí-Ibáñez

Adaptable as mother's "basic" dress...

DRYCO®

suited to a variety of infant formula needs

DRYCO continues to prove its usefulness as a flexible formula base for all infant feeding needs—for normal infants, for prematures, and especially when digestive disturbances demand low fat.

DRYCO is high in protein, but low in fat and moderate in carbohydrate. Made from specially selected pasteurized whole and skim milks of superior quality, and fortified with vitamins A and D, DRYCO is readily digested and easily reconstituted with warm or cold water. Available through all drug channels, in 1- and 2½-lb. tins.

For samples and special formula suggestions for use with prematures and in the treatment of vomiting or diarrhea, write to:

Prescription Products Division
The BORDEN Company
350 Madison Ave., New York 17

International

RECORD OF MEDICINE

VOL. 167 NO. 4 • WHOLE NUMBER 2854 • APRIL 1954

The Search for the Philosophical Nature of Disease in the History of Medicine

AN INTRODUCTION TO HANS SELYE'S "SKETCH FOR A UNIFIED THEORY OF MEDICINE"

The noblest preoccupation of the physician throughout history has been to establish a unified concept of the nature of disease. From Hippocrates to Sydenham the task of the physician was to *describe* what he observed in his daily practice. *Experiment*, that supreme instrument of the clinical researcher, appeared very late in history. It started with Roger Bacon in thirteenth century England, was later introduced by Galileo into the field of natural sciences, and ultimately was raised to a philosophical category by Francis Bacon. Ever since then visual observation in the Goethan sense has been closely linked to that sovereign questioning of Nature which is experiment. Man has been pressing Nature to answer basic questions concerning its most secret biopathological motives.

Pre-Hippocratic medical thought was motivated by a terror of the unknown. The nature of disease was thought to be demoniac by the Chaldeo-Assyrian civilizations. Hippocrates introduced the first naturalistic concept of disease by analyzing each patient as a natural phenomenon subject to the laws of space and time which govern all life. His humoral theory of disease had been preceded by Empedocles' concept of disease as an imbalance among the four basic elements (fire, air, water, and earth) of life and was followed by the theory of Asclepiades of Bythinia, who considered disease as a disturbance in the mechanics of our atoms.

Two centuries after Christ, Galen made of the *pneuma* the essential principle that maintained organic equilibrium. Later, in the Renaissance, Paracelsus considered man a microcosm, a constellation subject to the influence of cosmic forces. Vesalius and Harvey were the heralds of a new anatomy and pathology based on genuine observation and experimentation. The avalanche of theories and systems that marked the seventeenth century—Galileo in physics, Van Helmont in chemistry, and Descartes and Bacon in philosophy—was followed by a revival of the Hippocratic spirit with Sydenham, who established the first natural history of diseases considered as natural processes. From then on there have been numerous attempts to unify the theories about the nature of disease. Stahl recreated animism; Boerhaave started true clinical observation; Morgagni emphasized postmortem anatomy; Haller described the sensibility and irritability of nerve structures; Bichat made organic lesions the basis of pathology; Laennec created organopathology; Virchow established local organic lesions as the cause of disease; Claude Bernard created physiopathology; and, under the aegis of Corvisart and Auenbrugger, clinical pathology was born.

Towards the end of the nineteenth century, Pasteur and Koch contributed their concept of bacteriological causality and Kretschmer his constitutionalist theory. We must also remember Bergmann's functional pathology, Brown Sequard's hormonal pathology, Frederick Kraus's neurovegetative pathology, Speransky's theory of neurodystrophy, Siebeck and Weizsacker's biographico-personal pathology, and the modern psychosomatic and anthropological concepts of disease.

The physician of today, heir to a rich historical tradition, regards the problem of disease not only as a study of syndromes and lesions, but mostly as an etiological question. He is interested not so much in the

pathogenesis of a disease as in its etiology, which is the principal basis of a truly scientific therapy. Disease has become a historical problem integrating time and environmental circumstances, and an anthropological question involving a philosophico-scientific concept of human life. The sovereign individuality of that pathographic story we call "clinical history" merges today with the universality of scientific knowledge, of which the clinical history is the true basis.

Today we know that disease does not exist outside the patient but is located *within* the patient, who is influenced by the confluence of his genetic constellation, his environment, and the interrelationship—whether voluntary (free will) or accidental (ecological influences)—between his being and its environment. Every disease is an evolutive process, a way of life, not a parasitic life grafted upon normal existence. Gregorio Marañón has said: "The brief paragraph devoted to the study of the *course* of disease in the Treatises contains for the most part the key to the concept of those diseases."

The greatest ambition of the modern clinician is to unify his ideas within a concept that will embrace all the etiopathogenic essences of disease considered as a form of life, as the way a being reacts to the *endogenous* influences (the cenesthesic reflections of his own body) and the *exogenous* influences (the pathogenetic interrelationships between the precipitating situation of the surrounding world and the individual organism) that act on him. The human being appears to the physician of our day as an entity situated in time and space—between *Nature*, which is his own organism plus the reality of the outside world, and *History*, which is the chronological evolution of his individual life and his historical reality.

Through his senses—the windows through which the outside world penetrates and acts on him—each being screens from the cosmos a fragment of the world. From the moment of birth, each being creates for himself a world of his own in which he lives, and from the sum of the stimuli he receives he forms his environment. In this sense, health and disease are modalities of the same physiological functions. All disease involves a vital teleological impulse towards cure. That is why modern biology, starting with von Uexkull, tends to reject the Darwinian concepts and creates not mere biological mechanics but authentic Biology. Modern biology tends to study not so much *organized* life, the use of organs, which is secondary life, as it does *organizing* life, which is basic primary life. Modern biology does not study the struggle for life, which is such an important factor in Darwinism; instead, it investigates those main factors of life which are the "strugglers" themselves. It studies that original *unorganized* life that creates organization. The human being thus becomes a system involving a series of reactional possibilities and capable of responding adequately to a series of *new* situations and variable—internal or external—tensions.

The philosophical objective of the modern physician is to learn how to read the secret of the nature and history of disease in the patient. He must therefore avail himself of a concept of the nature of disease. Half a century ago the Spanish pathologist León Corral said that disease is "*an abnormal way of life* in which the organism reacts against some harm." For, paradoxically, the essence of Physiology is really Pathology, just as the most typical features of our face are those which can be exaggerated in caricature.

And in answer to this deep-rooted desire of the medical researcher throughout history to integrate his knowledge within a framework of a philosophical doctrine, Hans Selye, creator of the theories of *stress* and the general adaptation syndrome which have so radically changed the picture of Endocrinology, has outlined a theory to unify medicine. The International Record of Medicine and General Practice Clinics proudly publishes in this issue Hans Selye's new theory concerning the nature of disease. This theory in a way binds together all the doctrines and concepts cited in this introduction, theories that represent the effort of human thought to arrive at an understanding of the nature, causes, and course of disease as the best way of knowing how to cure it.

We reserve evaluation of this theory for another article. Our only purpose here is to set the theory within the framework of earlier medical philosophies.

There are still people who look upon theories with a contempt that comes from that excess of pragmatism so prevalent in modern medicine. But we must respect theories, for they have provided the bases for the most important practical discoveries. Leonardo da Vinci understood that when he said: "*La teoria è il capitano, la pratica sono i soldati.*" "Theory is the captain; practice, the soldier." In the case of Hans Selye, however, both the concept of *stress* and his theory unifying medicine represent a harmonious flight of philosophical thought made on reliable wings of experimental research and clinical observation.

Félix Martí-Ibáñez, M.D.

Sketch for a Unified Theory of Medicine*

Hans Selye, M.D., Ph.D., D.Sc., F.R.S. (C.)

INSTITUTE OF EXPERIMENTAL MEDICINE AND SURGERY, UNIVERSITÉ DE MONTRÉAL
MONTREAL, CANADA

Introduction. Summary of earlier views on stress and disease. Search for further unification. What is apparently distinct and in need of unification? Health and disease. Disease itself and its signs or symptoms. Specific and nonspecific phenomena. Qualitative and quantitative differences. Units and complexes. How could the stress concept lead us to a more unified interpretation of medicine? Stress and adaptation. Stress and growth. Stress and specificity. The functional unit of life. Apologia of teleologic thought in biology and medicine.

INTRODUCTION

In all the volumes of the "Stress" series,[1,2,3,4,5] we attempted to use the adaptation-syndrome concept as a basis for a sketch of a unified theory of medicine. Of course, any attempt at a perfect unification would be *a priori* doomed to failure, since the various diseases differ both in their pathogenesis and in their manifestations; hence, they could never be reduced completely to any one common denominator. Nevertheless, efforts to arrive at a unified concept of disease have been made by physicians ever since the beginning of medical history. Whenever objective observation revealed any one structural or functional characteristic to be common to all the parts of the body, or to all of its diseases, efforts were made to single out this characteristic as a lookout post from which to obtain a co-ordinated view of medicine as a whole.

If we do not go any further than this, if we do not look upon these constructions of the mind as anything more fundamental than an elevated position from which we can get a synoptic view of disease, such efforts are, to our mind, quite permissible.

In our *First Annual Report on Stress*,[2] where we attempted to explore possibilities in this direction, we expressed our views as follows:

"Whenever a large number of facts accumulates concerning any branch of knowledge, the human mind feels the need for some unifying concept with which to correlate them. Such integration is not only artistically satisfying, by bringing harmony into what appeared to be discord, but also practically useful. It helps to see a large field from a single point of view. When surveyed from a great elevation some details in the landscape become hazy, or even invisible; yet, it is only from there that we can see the field as a whole in order to establish where more detailed exploration of the ground would be most helpful for its further development."

Since stress plays an important part in so many diseases and since the L-A-S and G-A-S can affect virtually every part of the body, it was rather tempting to use stress as a basis for some degree of unification.

* This article is based on original observations, which are described in further detail in the *Third Annual Report on Stress*,[4] and essentially represents a summary of thoughts based on factual data described in that volume.

SUMMARY OF EARLIER VIEWS ON STRESS AND DISEASE

In the earlier volumes of this series, we developed our concept of disease to a point which has been illustrated by a schematic drawing, figure 1.

In this way, a somewhat more unified concept of pathology began to take shape. The most varied manifestations of disease were considered to have a tripartite pathogenesis, consisting of: (1) the direct action of the exogenous agent, (2) endogenous factors, which inhibit this action, and (3) endogenous factors, which facilitate this action.

Each of these three components must always be analyzed: it is not enough to diagnose a condition as inflammation and to prescribe an antiphlogistic hormone if we wish to use this concept as a guide to therapy. It may be apparently quite logical to treat a case of, say, acute appendicitis or of tuberculosis with cortisone, because these are manifestly inflammatory lesions and the hormone is an anti-inflammatory one. However, an analysis of the entire pathogenic situation can prevent such grave errors. It will show that in these instances, inflammation is a useful phenomenon necessary to put up local resistance to the otherwise highly damaging topical stressors, the microbes. Here the principal pathogenicity of the evocative microorganisms does not lie in any tendency to elicit excessive inflammation. On the contrary, only too often they do not produce a sufficiently strong inflammatory barricade which could prevent their tissue-damaging effects and their spread throughout the body.

In essence, stress therapy (treatment with adaptive hormones or nonspecific therapeutic agents) is a "tactical therapy," such as was practiced hitherto almost exclusively in surgery. There, it was always customary to use it whenever the causative pathogen could not be eliminated. For instance, when an inoperable neoplasm occludes the gut, the surgeon makes an artificial opening to by-pass the obstruction. This is no cure but it helps the patient to live with his disease in

GLOSSARY

To correct for the necessity of using symbols instead of the lengthy and cumbersome technical designations currently employed in stress research, the following key may be helpful.

A-C—*Antiphlogistic corticoid.* Corticoid particularly effective in inhibiting inflammation. Same compounds also have G-C effect.

ACTH—Adreno corticotrophic hormone or corticotrophin.

G-A-S—*General Adaptation Syndrome.* A triphasic, nonspecific, adaptive reaction comprising: (1) the alarm reaction, (2) the stage of resistance, (3) the stage of exhaustion.

G-C—*Gluco-corticoid.* Corticoid particularly effective in raising the liver glycogen and blood-sugar concentration (e.g., cortisone, hydrocortisone). Same compounds also have A-C effect.

L-A-S—*Local Adaptation Syndrome.* A triphasic, nonspecific, local adaptive reaction comprising topical regressive (degeneration, necrosis) and progressive (inflammation, hypertrophy, hyperplasia) changes.

M-C—*Mineralo-corticoid.* Corticoid particularly effective in causing sodium retention and potassium loss (e.g., desoxocortisone, electrocortin). Same compounds also have P-C effect.

P-C—*Prophlogistic corticoid.* Corticoid particularly effective in facilitating inflammation. Same compounds also have M-C effect.

STH—Somatrophic hormone or "growth hormone."

The "*Granuloma-pouch*" is made by injecting a given amount of air subcutaneously. This is followed by injection of an irritant, e.g., croton oil, into the regular ellipsoid chamber so formed. The irritant transforms the connective-tissue lining into a granulomatous barrier, while the air is gradually replaced by fluid exudate.

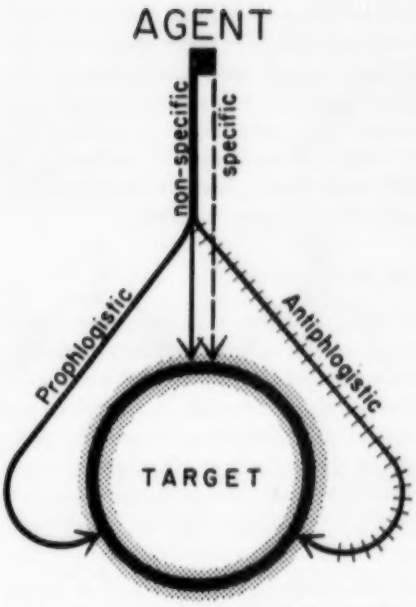


FIG. 1. All **agents**, which act upon the whole body or any of its parts **(target)**, exert dual effects:

(1) Specific actions **(interrupted arrow)**; for instance, ether causes anesthesia, *Salmonella typhi* produces typhoid fever.

(2) A nonspecific stereotypical reaction of stress, which manifests itself in the form of the general adaptation syndrome **(three-branched arrow)** Stress affects the target directly. The topical tissue injury caused by a burn, the immediate effects of microbes upon cells are cases in point **(straight branch of solid arrow)**, but some of its actions are mediated through humoral or nervous pathways **(curved branches of this arrow)**.

The principal humoral pathways lead through the anterior pituitary and the adrenal cortex, which produce essentially "adaptive" hormones. Among these, ACTH and the **antiphlogistic-** corticoids (e.g. cortisone) inhibit; STH and the **prophlogistic-**corticoids (e.g. DCA) stimulate inflammatory responses to injury.

The most prominent reaction patterns to topical stress are inflammation and necrosis, to systemic stress, "shock." Various combinations of these basic responses constitute the essence of most diseases.

The regulation of tissue reactivity, for instance through adaptive hormones, often determines whether the body succumbs to disease or resists a potential pathogen by means of adaptation. Other humoral agents and the nervous system also participate in the adaptation syndrome, but the nature of their pertinent actions is not yet sufficiently understood to permit a detailed consideration at the present time.

All the effects of biologic agents, and particularly those of the adaptive hormones, largely depend upon "conditioning factors" **(shaded area)**, some of which are external (diet, temperature, light), others internal (heredity, constitution, previous exposure).

Thus, a state of stress is produced in the body through multiple pathways, its effects being always modified by the variable specific actions of the eliciting agent and by the conditioning factors (the "constitution" or "terrain") which are different in every individual, in every part of the individual. These factors can affect target and pathway selectively, and thereby vary the manifestations of what, in essence, is but a single stress response. (After Selye and Horava[4])

relative harmony. Thus, we accomplish by purely mechanical means what stress therapy achieves through biochemical processes.

Stress therapy is *not offensive;* it is not specifically directed against any one pathogen (as are antisera or chemotherapeutic agents).

Stress therapy is *not symptomatic, nor strictly substitutional;* it does not act by merely eliminating any one specific symptom (e.g., a headache with aspirin) or patching up a defect (e.g., a loss of skin with a graft, a lack of vitamin with a curative amount of it).

Stress therapy is rather *tactically defensive*, in that it adjusts active demarcation (barricading) and passive submission (topical death and spreading of pathogen) in a manner favorable to the organism as a whole.

Some agents are virtually "unconditional pathogens," in that their influence upon the tissues is so great that they cause disease almost irrespective of any conditioning or sensitizing circumstances (e.g., x-rays, severe thermal or mechanical injuries and certain microorganisms to which everyone is susceptible).

Most disease-producing agents, however, are to a greater or lesser extent, "conditionally acting pathogens": that is, they cause maladies only under special circumstances of sensitization. Their pathogenicity may depend upon genetic factors, the portal of entry through which they are introduced into the body, the previous weakening of resistance through malnutrition or cold, et cetera. Here, it is often impossible to decide which, among the many factors necessary for the production of disease, is the pathogen and which the conditioning factor, because the full pathogenic situation must be realized before the malady can become manifest.

SEARCH FOR FURTHER UNIFICATION

This interpretation was still not wholly satisfactory as a unifying concept of disease, primarily because it failed to encompass the noninflammatory maladies. With the characterization of the L-A-S it became evident, however, that local stress produces not only inflammation, but also degeneration, necrosis, hypertrophy and hyperplasia. All of these changes can be regulated by prophlogistic and antiphlogistic hormones whose actions (as well as the corresponding effects of vasoconstrictor and vasodilator nerves) might therefore be viewed more properly as favoring or inhibiting *reaction to injury in general*. Hence, the concept need not be restricted to the inflammatory diseases.

The question remains, however, whether the manifold specific effects of agents could also be integrated into this concept. These appear to be qualitatively different both from each other and from the nonspecific (stress) effects; apparently, they do not lend themselves to a unified interpretation. If we could somehow also express specific actions in terms of stress, all disease manifestations would be reduced to a common denominator. They would result from different proportions of the aforementioned three fundamental pathogenic factors:

(1) the stressor,

(2) proreactional factors, and

(3) antireactional factors.

Apart from the relative proportions between these three components, the manifestations of maladies would then only depend upon *when, where, and how much*, this same triad develops. That is, upon:

(1) **time** (the duration and possibly repetitive nature of stress);

(2) **space** (the location of the target or targets); and

(3) **intensity** (the degree of activity, at which any given proportion between the above mentioned three fundamental pathogenic factors could act).

In the past year, one of my co-workers attempted to formulate the conceptual foundation for this view through the "reacton" theory. The latter was discussed at length in two special reports[4, 6, 7] upon which the following outline is based. By way of an introduction, let us state at once, however, that we believe the common denominator between the manifold specific and nonspecific actions to be that they all are merely mixtures of the same kinds of elementary responses.

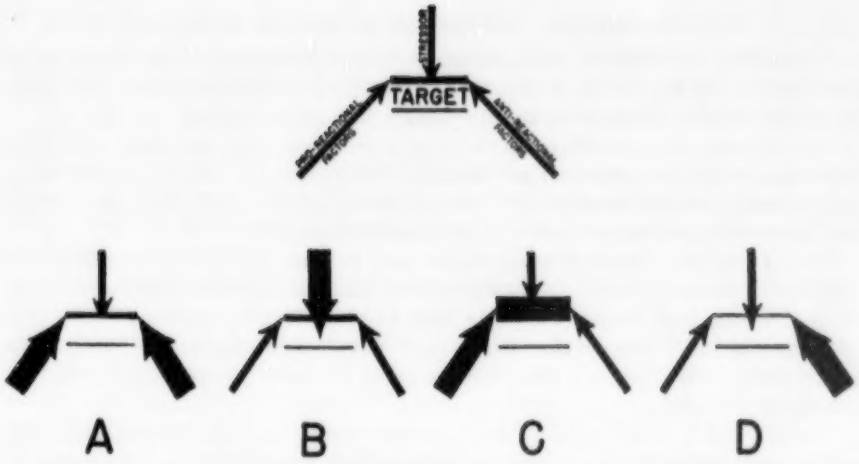


FIG. 2. **Schematic illustration of relationship between target, stressor, proreactional and antireactional factors.** The top diagram shows the basic relationships under standard conditions. The stressor is directed against the target but does not actually penetrate into it here, since it is not strong enough to overcome the resistance of the target's reactive surface (e.g., an inflammatory barricade). **A.** Both proreactional and antireactional factors are excessively developed, hence, the condition of the reactive surface remains unchanged. The mild stressor again fails to penetrate into the target. **B.** Proreactional and antireactional factors (and thus the reactive surface) are normally developed, but the stressor is of excessive intensity, so that it penetrates into the target. **C.** Proreactional factors are overabundant, and, therefore, the reactional surface hypertrophies in excess of the stressor's requirements; consequently, the latter is far from penetrating into the target. **D.** Antireactional factors are unduly active, hence, the reactional surface is so weak that even the mild stressor readily penetrates into the target. (The granuloma pouch can serve as an experimental model in which all these relationships have actually been verified. In the basic sketch on top, read: **target** = skin; **reactive surface** = granulomatous barricade (formed from the connective tissue separating the derma from the local stressor); mild **stressor** = dilute croton oil; **proreactional factor** = STH; **antireactional factor** = cortisone. Dilute croton oil does not penetrate into the skin sufficiently to cause necrosis under normal conditions. **A.** The situation is unchanged because both STH and cortisone levels are proportionately raised. **B.** The granuloma is penetrated and the skin becomes necrotic because concentrated croton oil is used and, to resist it, a normal balance between proreactional and antireactional factors does not suffice. **C.** Excessive amounts of STH are given, although the stressor is only dilute croton oil. The granuloma is far in excess of what would be required, and, hence, the great inflammatory response itself is the major manifestation of "disease." **D.** Cortisone is given in excess, therefore, virtually no inflammatory barricade develops, so that even dilute croton oil penetrates into the skin and causes necrosis.)

Although biologic reactions tend to give the impression of oneness, they actually represent mosaics of simple activation and/or inhibition (stress) in a great variety of pre-existent elementary, subcellular biologic units—the "reactons." Each of these is capable only of one kind of response, but by blending these elementary reactions in different combinations, qualitatively distinct aggregates result.

To illustrate this by an example, let us remember that one can create a virtually unlimited variety of melodies on the keyboard of a piano by merely "activating" or "inhibiting" its chords, varying time, site, and intensity of simple touch on preexistent keys, each capable only of one kind of response. We hope to show that "reactons," not cells, are the elementary "keys" of living matter and that all the manifestations of normal and pathologic life depend only on when, where, and how much (or how many of) these biologic elements are stressed.

WHAT IS APPARENTLY DISTINCT AND IN NEED OF UNIFICATION?

In thinking about the fundamental nature of any phenomenon, the human mind invariably tends to analyze it from two essentially distinct viewpoints. We want to know its causal connections and its primary constituent element.

For instance, if an intelligent member of a primitive tribe were first confronted with an automobile, he would ask himself, "Who made it?" (that is to say, what is its cause?) and, "What is it for?" (that is, what can it cause?)—but also, "What is it made of?" (that is, what are its constituent elements?).

This innate quest for the Primary is also quite evident during the period of mental awakening in every child. It manifests itself by what might be called the "serial why," which leads to the following type of conversational pattern: "Why is it dark at night?" "Because the sun sets." "Why does the sun set?" "Because the earth turns away from it," and so forth, until the hard-pressed adult succeeds in changing the topic.

Our craving to climb up along such question-ladders does not diminish with maturity; only our hopes of reaching the top rung fade away with age, for we come to realize that it is just as inherent in human nature to be blind for the Primary as it is to look for it. Yet, as soon as man understands that, for him, the ladder of comprehension has no end, he can find comfort in the realization that consequently, there also is no limit to his possible progress; no matter how advanced his wisdom, he always remains capable of yet another step forward.

Except for a few remarks in the chapter on teleologic thought, we have little to say about primary causes in medicine, but our experimental work has led us to a point where we feel that a better understanding of the primary elements of disease could be of great assistance in sketching a more unified picture. Before attempting any further unification we must now outline what strikes us as being especially in need of it.

What are those concepts of medicine whose distinctness is in question? In the chapter "Definitions and Terminology" of our *Third Annual Report on Stress*,[4] we tried to characterize some of them and many more could be mentioned. Here, we shall merely select five pairs of twin concepts, because they are rather basic in biology and medicine and because, at first sight, they appear to defy any effort of being reduced to a common denominator.

(1) **Health and disease.** Textbooks usually define health as the absence of disease, and vice versa. The two conditions are alleged to be opposites of each other. Is this really so? Are they not rather different only in degree and in the position of vital phenomena within time-space?

Hemorrhage, inflammation, loss of weight or a rise in temperature could be mentioned as typical manifestations of disease, in that they supposedly represent a deviation from the condition of health which we call the norm. However, menstruation is accompanied by hemorrhage and inflammation, yet the failure of its occurrence is what we would call a disease in a young adult woman. If she menstruated excessively or from any place other than the uterus (e.g., in endometriosis), that would also be a disease, as would be menstrual bleeding at an abnormal time (e.g., in precocious puberty).

A loss of weight, a variation in temperature can likewise be considered as pathologic only in relation to some norm of health, but even health and biologic normalcy are not synonymous. An individual born with an undeveloped toe or with a disfiguring scar across his face is neither normal nor unhealthy. A defect is not a disease.

It may be argued that the examples given—hemorrhage, inflammation, loss of weight, a rise in temperature—are merely manifestations of disease and not disease itself. Perhaps we should distinguish between disease and the signs or symptoms of disease.

(2) **Disease itself and its signs or symptoms.** The dictionaries say that disease is "a definite morbid process having a characteristic train of symptoms. It may affect the whole body or any of its parts, and its etiology, pathology and prognosis may be known or unknown." On the other hand, a symptom is "any functional evidence of disease," while a sign is "any objective evidence of disease" (Dorland's Medical Dictionary).

This point of view, though quite generally accepted, is hardly satisfactory to the analytical mind. Is the high blood pressure of essential hypertension a disease or a sign? If it is a disease, it is also its own sign, and, if it is a sign, of what is it a sign? The same doubts arise in connection with nephritis or pneumonia. These conditions could be called diseases, while their consequences (e.g., proteinuria and hypertension with nephritis, fever and dyspnea with pneumonia) might be regarded as their signs. Yet, if the same renal and pulmonary changes happen to develop in the course of scarlet fever, for example, then they are no longer considered to be diseases in themselves, but signs of the latter malady.

Actually, we have a generally subconscious but very practical reason which largely justified this usage. When we speak of disease, we actually mean that there is no hope in the light of available knowledge of ascending any higher in the causality chain of the condition before us. When we speak of a sign, we mean that there is hope that we could climb at least one rung higher towards the understanding of the primary cause.

Thus, when we compare the concept of disease with that of the symptoms and signs, the difference does not appear to be essential, and we are tempted to ask whether some unifying interpretation of these derangements could not help us to arrive at a more fundamental understanding of morbid phenomena. Of course, when it comes to signs and symptoms, the first preoccupation of the physician is the degree of their specificity, that is their reliability as indicators of any one disease.

(3) **Specific and nonspecific phenomena.** The original meaning of the term specific is "that which characterizes or constitutes a species." For instance, we speak of the specific difference between the dog and the wolf.

The concept of specificity is of particular importance in stress research, since we have defined biologic stress as a condition elicited by preponderantly nonspecific agents, that is, agents acting on many targets without selectivity. By contrast, a specific agent acts only on one or a few targets and, therefore, provokes selective effects. Thyrotrophic hormone has been mentioned as an example of a specific agent because few, if any other, substances share its selective action upon the thyroid

epithelium. Conversely, many of the changes elicited by pyrogens are rather nonspecific, since they can be duplicated by numerous other agents. Yet, it would be difficult to mention any example of an absolutely specific or absolutely nonspecific agent.

Here again, we gain the impression that the two partners of the conceptual pair, specific and nonspecific, are only apparently different in quality but actually distinct only in degree, that is in quantity.

(4) **Qualitative and quantitative differences.** This brings us to the very crucial problem of distinguishing between qualitative and quantitative differences in general. One would think that the actions of a mild and a potent pressor substance differ only in degree (quantity) while, for instance, the diametrically opposed effects of a nervous excitant and a depressor drug differ in quality. However, this distinction appears to be self-evident, only because of the terminology used. Speaking about excitation and depression implies that we view these conditions from an intermediate level, which we recognize to be the "norm." If we begin from absolute lack of activity, we can construct an ascending scale, which rises from zero, through increasingly less pronounced degrees of "depression" to "excitation."

It is perhaps not wholly unjustified to ask whether qualitative and quantitative differences are not likewise merely a matter of degree and of the distribution pattern of vital phenomena in time and space. One could imagine, for instance, that the impression of virtually any qualitative difference could be created by mere combinations and permutations of induced activity in a limited number of biologic elements, each capable only of a single kind of response.

This brings us to the last and perhaps the most important twin concept, which we shall have to analyze before attempting to arrive at some unified interpretation of biologic phenomena, namely, the problem of the fundamental unit of life.

(5) **Units and complexes.** The difficulty of drawing a sharp distinction between units and complexes is, of course, by no means particular to biology and medicine. We encounter it in chemistry, physics, algebra and geometry. We speak of a unit of matter or of energy; a number can be taken as a unit and so can a certain element of structure or form. To mention a classic example, the atom has long been considered to be the unit of matter. However, in view of recent progress, particularly in physics and mathematics, this apparently indivisible elementary building block has been shattered and from its fragments emerged the most universal theory of unification which the human mind has yet been able to create. And still, the atom is a unit. Only it is not the ultimate or fundamental unit. In biology, a species is a unit among living forms and so is an individual within this species, an organ within this individual, a tissue within this organ, or a cell within this tissue. Traditionally, the cell has been considered to be the primary or fundamental unit of life and, yet, it is still a highly complex aggregate.

In the following section, we shall explore to what extent the stress concept could help us to breach the gaps between the aforementioned basic concepts of biology and medicine: health and disease, disease and its symptoms, specific and nonspecific changes, qualitative and quantitative differences, and, most fundamental of all, units and complexes.

I do not know—nor does it really matter—whether the basic arguments in support of my views have already been expressed by philosophers. Probably they have. Priority of discovery in the sense in which it exists in the natural sciences hardly has a true counterpart in the science of thought itself. Every pattern of argument, compatible with the structure of the human brain, has probably been formulated at some time, in some language or form, by some author, especially in regard to such basic principles as those with which we shall have to deal. But there is a great difference between a thing that has been seen (or even described) and one that is known to those whom it concerns. The basic procedures of reasoning are equally applicable to all sciences, yet in order to use them for the creation of new knowledge and understanding which is in any one domain, they must first be translated into a language which is understood and accepted by the workers in that particular field. To us, biologists and physicians, generalizations are acceptable only if they are demonstrably substantiated by many measurable individual data. We instinctively shy away from philosophic arguments, because the mind works much more rapidly than the hand, and as soon as we risk formulating some generalizations about science, we realize that the laboratory cannot keep pace with imagination. Ours should really be an experimental philosophy, since it is only the teachings of objective observation that we can really assimilate. As its natural counterpart, such an experimental philosophy would create a theoretic medicine which, I believe, could become just as enlightening and practically useful to us physicians as theoretic physics has been to our colleagues in the exact sciences.

To lay the foundations for this will necessarily be a time-taking endeavor, likely to require the concerted efforts of several generations. The following pages can be regarded only as a very tentative and hesitating attempt to draw a few lines for a preliminary sketch.

HOW COULD THE STRESS CONCEPT LEAD US TO A MORE UNIFIED INTERPRETATION OF MEDICINE?

(1) **Stress and adaptation.** Our earlier work on the general adaptation syndrome and, particularly, the more recent observations on the local adaptation syndrome, brought out clearly the essential difference between "specific resistance" and "crossed resistance." They convinced us of the necessity to distinguish between three fundamentally different types of adaptation:

(A.) **Homotropic adaptation,** that is, a simple, progressive adaptive phenomenon, which can be accomplished by mere hyperplasia and hypertrophy of pre-existing cell elements, without qualitative change. This response is elicited whenever a tissue is only required to increase its activity, regarding a function to which it is already adapted at the onset. Such pre-existent adaptation can be the result of phylogenetic and ontogenetic development (e.g., a muscle cell forced to perform more than the usual amount of contractile activity), or of previous adaptive transformations (e.g., a macrophage formed from undifferentiated mesenchyme under the influence of India ink, which is now forced to engulf additional amounts of the same substance). The purely morphologic aspects of this are sometimes designated as "prosoplasia."

(B.) **Homoiotropic adaptation** is called forth whenever a tissue adapted to one function is called upon to perform a slightly different, but cognate activity (e.g., a macrophage adjusted to the phagocytosis of kaolin particles, which is brought in contact with carbon particles).

(C.) **Heterotropic adaptation,** in which a tissue, fully differentiated for one type of action, is forced to readjust itself completely to an entirely different activity (e.g., transformation of a muscle cell into a polynuclear, phagocytozing giant cell). The purely morphologic aspect of this is "metaplasia."

In general, it may be said that the more a cell differentiates for a certain function, the less is it capable of heterotropic adaptation. Usually, the latter requires more or less complete dedifferentiation to a rather embryonic celltype, since fully differentiated cell-forms can rarely transform themselves directly into one another. Mitosis is the most effective way of regaining full, juvenile adaptability, by divesting the cell of all its differentiation. Interestingly, mitotic proliferation is also rarest in the most highly differentiated celltypes.

Above we discussed the three types of adaptative phenomena principally in connection with topical stress. It is evident, however, that this same classification is also applicable to systemic reactions, since these are essentially composed of multiple topical responses, integrated throughout the body by nervous and humoral means. It will be observed that from the simplest homotropic to the most complex heterotropic, these adjustments are effected by varying proportions of simple growth of pre-existent tissue on the one hand, and qualitative transformations into new kinds of tissue on the other.

These morphologic characteristics of adaptive phenomena have their equivalents in terms of biochemistry. Simple anabolism (the mere addition of more of the same material) suffices for homotropic adaptation, while more or less complete transformation of chemical constitution is usually necessary to affect heterotropic adjustments. Dedifferentiation appears to be a necessary intermediate not only for the morphologic but also for the chemical processes of "transadaptation."

The catabolism which occurs both in topical and in systemic shock is, in a sense, a "chemical dedifferentiation." It is through the lysis of cellular material (histolytic phenomena in the L-A-S, loss of body and organ weight in the G-A-S) that chemical substances are liberated, which can then serve as building blocks for the neoformation of tissues better adapted to new requirements.

This section on stress and adaptation revealed certain aspects of unity in apparently diverse vital phenomena. The chief unifying principle, in the emerging impression of "oneness," is the basic reactiontype to stress, with its concomitant adaptive responses. Yet, we are still far from understanding that which meanwhile remains a simple impression of some fundamental unifying law. As the picture stands at this point, perhaps its most disturbing feature is the difficulty of correlating the "pathologic" phenomena of transformative adaptation (e.g., inflammation) with the "physiologic" type of simple evolution towards a certain pattern of relative organ-growth. The latter appears to be directed by the laws of heredity, without any manifest dependence upon stress.

(2) **Stress and growth.** It is noteworthy that the so-called "adaptive hormones" are also important regulators of systemic growth. ACTH and the A-Cs (cortisone, hydrocortisone) are potent growth inhibitors, while STH is so effective in the opposite sense that it has actually been called "the growth hormone." It is in agreement with expectations, therefore, that stress itself can affect the growth of the body as a whole. Systemic stress has a marked growth-inhibiting effect. At least in part, this is mediated through ACTH and the A-Cs.

But is there any link between stress (or adaptive hormones) and that selective topical growth of certain parts, which leads to qualitative changes in morphogenesis? Of course inflammation, one of the most salient features of topical stress, is accompanied by particularly pronounced local, proliferative growth phenomena, which are often homotropic (e.g., simple proliferation of pre-existent fibroblasts). Other examples in point are, selective lympholysis caused by systemic stress or by antiphlogistic hormones and lymphatic hyperplasia after STH treatment.

Little is known, as yet, about the possibility of producing regional growth in certain areas with the aid of topically applied STH, but it is undoubtedly possible to induce a marked selective growth inhibition by the local application of hydrocortisone to certain predisposed regions. Thus, the development of one paw, one ear, the snout, or a specifically sensitized skin region can be greatly inhibited by topical treatment with hydrocortisone (cf. *Second Annual Report on Stress*[3] and *Third Annual Report on Stress*[4]).

In many of these instances, the topical effects of hormones, either upon inflammation or upon growth, are manifest only under certain conditions. For instance, systemic stress or local vasoconstriction sensitizes to the topical effects of catabolic (antiphlogistic) hormones, while freedom from systemic stress or local hyperemia enhances the topical actions of anabolic (prophlogistic) substances. It has become a major branch of stress research to explore the mechanism through which these "conditioning factors" alter regional tissue reactivity to hormones (for reviews see "Stress," *First Annual Report on Stress* and *Third Annual Report on Stress*).

It is also possible that, during topical stress, certain cells may develop a special affinity for growth-regulating adaptive hormones, although the available bioassay methods have not yet permitted us to establish this with certainty.

All these factors could endow certain tissue regions with a selective sensitivity for one or the other type of adaptive hormone and, thus, permit the participation of stress in localized tissue-growth phenomena.

Perhaps the most important topical stimulant of growth is activity. A muscle cell, forced to perform much contractile work, or a glandular cell, stimulated to excessive secretory activity, will undergo hypertrophy. Could the "stress" of local hyperactivity itself act as a "conditioning factor" for growth-regulating adaptive hormones? By calling this "stress" we may appear to obscure the limits between specific and nonspecific actions, a distinction which is the very basis of our stress theory.

With this in mind, let us now re-examine the relationship between stress and specificity.

(3) **Stress and specificity.** If stress is defined as a nonspecific action-reaction phenomenon, then adaptive tissue-growth, elicited by highly specific stimuli, cannot be so designated. Thus, the selective hypertrophy of a muscle caused by frequent stimulation with its specific physiologic excitant, the motor-nerve impulse, is certainly not a stress reaction in the usual sense. It is equally evident, on the other hand, that such specific muscular activity, if excessive, can cause local damage to the muscle itself, as well as systemic stress, with the accompanying manifestations of the G-A-S, for instance, an ACTH discharge, lymphatic involution or gastrointestinal ulcers. What then, is the relationship between the specific and the nonspecific in such responses?

This leads us to the frequently discussed, but still quite cryptic question of the "first mediator" of stress reactions.

A localized tissue-injury (e.g., one caused by a burn or croton oil), if sufficiently severe, produces not only topical manifestations of the L-A-S, but also a mobilization of systemic defense through the G-A-S. Yet, we still do not know through what mediators the impulse is carried from the site of injury to distant parts of the body, for instance, to the pituitary-adrenal axis. The integrity of the innervation in the injured area is not essential, since damage to a completely denervated limb can still elicit a G-A-S. Therefore, humoral stimuli alone appear to be adequate for the generalization of topical stress responses, but of course, nervous stimulation can also act as a systemic stressor.

The humoral transmittor substance, or substances, in question have been described, provisionally, as the "first mediator(s)." Various investigators considered the possibility that locally produced nonspecific products of tissue catabolism, polypeptides, histamine, histamine-like compounds, adrenergic or cholinergic substances might be the "first mediator." It has been demonstrated beyond doubt that a G-A-S can be produced with any one of these compounds, but all efforts have failed to prove that one of them is the only "first mediator" of all stress reactions. Indeed, it is even possible that the mediation is not due to the presence of humoral substances, but rather to the lack of some vitally important blood constituent, which might be avidly used up by damaged tissue, to the detriment of the organism as a whole.

In the genesis of inflammation, "mediators" have also been postulated. Here again, polypeptides (e.g., leukotaxin), histamine, histamine-like substances, and many other alleged regulators of the inflammatory process were the subjects of much study. The fact that a stimulus for inflammation can be thus transmitted by humoral means is definitely established. To take but one example, the exudate which accumulates in a granuloma pouch, produces inflammation in connective tissue wherever it is injected. Indeed, we found it possible to first produce exudate (with the minimum effective dose of croton oil, in a granuloma pouch) and then to transmit inflammation with it through several animal passages. Fluid formation in response to injected exudate remained strong, even after three or four transfers. By that time the original irritant (croton oil) was diluted so much that it could no longer be responsible for the inflammatory reaction. Hence, some humoral transmittor must be postulated, but the nature of this "phlogistic mediator" remains unknown.

The question now arises whether the "first mediator" of the G-A-S (the endogenous stimulus which transmits the stress message from the injured region to the whole organism, and particularly to the pituitary) could be the same as the "phlogistic mediator" of the L-A-S (the endogenous stimulant of inflammation). Injection of exudate is highly effective in producing a systemic alarm reaction with pronounced ACTH discharge. Perhaps the products of tissue injury and tissue activity, if formed in sufficient concentration, are responsible not only for topical defense (L-A-S with inflammation) but, if also absorbed in sufficient concentration, they could even alert the whole organism (by eliciting the G-A-S). None of the data available at present disproves the possibility of such a close relationship between local and systemic stress responses through the same system of mediation.

With this in mind we might now reconsider the somewhat confusing point raised at the end of the preceding section on "Stress and Growth." Is there any relationship between nonspecific stress and specific adaptive growth (e.g., of a muscle specifically stimulated by motor impulses)?

In this connection, let us recall that intense overexertion of a muscle can produce a true myositis. Indeed, if such a muscle is subsequently exposed to topical irritants, it reveals a marked change in nonspecific local reactivity,[8] phenomena which we would interpret today as "crossed resistance" or "crossed sensitization." Thus, specific stimulation of a target to perform its physiologic work can act as a topical phlogistic (topical stressor) stimulus, at least at certain dose levels. Of course such specific physiologic stimuli can also cause work hypertrophy. Thereby work predisposes the target to the homotropic (simple-adaptive-growth-stimulating) actions of anabolic hormones, for instance of STH.

Another relevant point is the relationship between specificity and quality of response. Nonspecific agents have been defined as stimuli "which affect many targets and are devoid of the ability to act selectively upon any one."[3] By definition the reverse is true of specific agents. Similarly, a nonspecific change is one which can be elicited by many agents, while a specific change can only be produced by one, or at least, a very limited number. The two appear to be quite unrelated and different in quality. Indeed, one has come to consider them as opposites.

The follicle-stimulating hormone is an example of a highly specific agent, since few, if any other stimuli share its power to exert a direct, selective stimulating effect upon the granulosa cells. Conversely, the production of an alarm reaction by exposure to cold is quite nonspecific, because numerous other stressors (trauma, infections, nervous stimuli) act this way.

Yet, even this fundamental difference between the specific and the nonspecific is perhaps more apparent than real. It has been shown for a great many reactive elements ("receptors" or "targets") that they can respond to irritation only in one manner. Their reactiontype is conditioned by their own structure, not by the stimulus which activates them, although they may be more sensitive to some agents than to others. Whether stimulated by heat, mechanical injury, or electricity, a muscle fiber reacts with contraction, an optic nerve fiber with the sensation of light, a glandular cell with secretion, and so forth. Could it be that the apparent multi-

plicity of "specific" reactions is merely due to combinations and permutations of such single reactiontypes, of which the various biologic elements of the body are capable? Should this be the case, then all the manifestations of life, from the regional to the systemic, from the entirely nonspecific to the most highly specific, could be brought down to a common denominator. They would merely represent various groupings of simple, qualitatively unidirectional, responses in the diverse biologic units (organs, cells, cell parts) of the body.

Thus, the fundamental uniformity of any vital response—growth and adaptation, reaction to topical or to systemic stressors—begins to emerge in a more definite form. One great problem that remains is the precise nature of the interrelations between the specific and the nonspecific responses. We believe that the understanding of this has been particularly handicapped by the general acceptance of the theory, which assumes that the cell is the ultimate unit of living matter. *Even a single cell can respond in qualitatively different ways. It would be difficult to understand this without assuming the presence within the cell of smaller units, which are still relatively independent of each other in their reactivity.*

(4) **The functional unit of life.** In 1667, through his primitive microscope, Robert Hooke, saw minute compartments in living plant tissues. These appeared to be empty spaces, separated by walls; he therefore called them "cells." Subsequently, it became evident that these cells are actually filled with what appears to be living matter, they contain a nucleus and cytoplasm. Yet, it was not until more than two centuries later that Schleiden and Schwann (1839) were struck by the fact that all living matter (including both plants and animals) is made up virtually of cells alone. This led them to propose the first great truly unifying scientific concept in biology, the so-called "cell theory." In brief, they assumed that the cell is the fundamental unit of all that is alive, somewhat as, for some time, the atom was considered to be the fundamental indivisible building block of matter.

The heuristic value of this concept for biology and medicine was as great as that of the atomic theory for chemistry and physics. Virchow's "cellular pathology" and many of our most fundamental biologic concepts were based on it. It is the essence of science to explore causal and topographic relations between units. No wonder that the recognition of a visible unit of life helped the progress of biologic science!

However, subsequent research revealed many facts incompatible with the cell theory of life. Certain slime moulds, for instance, grow to considerable size and, although they contain nuclei, they show no sign of a subdivision into cells. Conversely, erythrocytes contain no nucleus. The configuration of viruses is even more remote from the cellular structure, still they do appear to be alive. And why should we consider intercellular substances as inanimate?

Despite these and many other facts, patently incompatible with the cell theory, the latter was so useful that it became too deeply ingrained in the minds of biologists to be displaced by any other concept; findings which did not fit into it were merely discarded as unimportant exceptions to the rule. After all, even the atomic theory, which postulated the inconvertibility of elements into each other, had its exceptions.

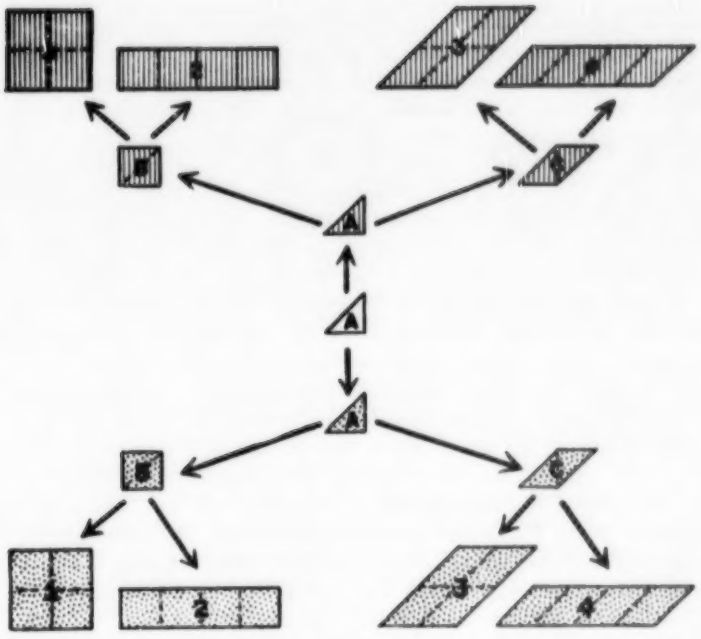


FIG. 3.—**Illustration of the view that "a specific element is the smallest part still specially fashioned for a certain composite structure."** The central blank "A" is a common element of "A" striped and "A" stippled. The latter differ from the parent structure in shading, not in form. A whole series of structures can be created, with any type of shading, by joining the element "A," and its increasingly more complex aggregates, in different ways. Thus in either series shown here, "A" is a specific element of "B," as well as of "C." "B" is a specific element of "1" and "2," but not of "3" and "4," since the latter could not be constructed from it. Let us emphasize particularly, however, that "A" is not a *specific* element of any among the structures "1," "2," "3," or "4," but only of their precursors "B" and "C" respectively, since it is only up to this level that the shape of the small triangle (dotted line) is still distinctly implied by the outlines of the whole. In the same sense, the specific element of a species is the individual (not the cell), that of a tissue is the cell (not the reacton) and the smallest, but still specific element of living matter is the reacton (not the atom). (After Selye;[6, 7] Selye and Horava[4])

However, as we now know, the atom is divisible and does not represent the fundamental unit of matter. Consequently, it has been possible to effect qualitative changes in elements—although they consisted only of one kind of atom—by rearrangement of their true fundamental units. For a very long time work along these lines was actually handicapped by the otherwise so fruitful, atomic theory of matter. Couldn't these same considerations also apply to the cellular theory of life?

In the passage on "definitions" (cf. p. 57 of *Third Annual Report on Stress*[4]), we already had occasion to mention that certain targets or receptors of biologic stimuli are of subcellular dimensions. It is inconceivable that the cell should be the fundamental unit of living organisms since, in a single cell, various portions can perform diverse vital functions independently and simultaneously (e.g., phagocytosis, secretion, perception, locomotion, digestion). An agent can undoubtedly influence one

part of the cell (e.g., an organelle), or one biochemical unit (e.g., an enzyme system), selectively. These elementary biologic targets—we called them[6] "reactons," in analogy with other elementary units (such as the nephron or neuron)—are perhaps also "alive." At least, in the absence of evidence to the contrary, we must consider this possibility, since they exhibit the features regarded as characteristic of life, just as the cell. Among other things, such reactons can grow and reproduce their own kind. They also have a great tendency to maintain their characteristic individuality, despite changes in the *milieu*, that is they are highly adaptable.

Let us point out clearly that nothing in our observations would justify the conclusion that these elementary targets are necessarily somatic structures, that is matter. It is equally possible that the reacton is only a focus of interrelations, a functional plan or pattern, which governs the organization of matter. A plan possesses, to an exquisite degree, such accepted characteristics of life, as the ability of growing, reproducing its own kind and adapting itself to changing requirements. The living is undoubtedly matter, but life is only one of its characteristics.

The great strength of the cell theory is that one can see the limits of these "building blocks" and demonstrate that, virtually all living matter is made up of them. However, this only shows that the cell is a morphologic unit, but is it the fundamental primary unit? The organs are units in the body, the tissues are units in the organs, the cells are units in the tissues, but why must we stop at this particular level in our analysis of living matter? The possibility of demonstrating clear borders by optic microscopy is hardly an adequate reason.

Where then, should we draw the line? Living, just as inanimate substance, consists of chemical elements, but these cannot be regarded as alive in themselves. They are units of matter, but not yet "live matter." Only certain combinations of the elements engender the characteristics of life. Then, why not recognize as the fundamental, specific elements of life, those smallest, organized structures, which still exhibit selective reactivity to biologic stimuli and manifest the generally accepted criteria of life?

Let us see now whether this theory of the reactons could help us to understand phenomena, which the cell theory does not explain.

The theory of the reactons postulates that:

(I) **The fundamental specific elements of life are of subcellular dimensions;** indeed they may not have visible limits, they may be merely focal points of interactions between the constituents in living matter. These "reactons" are defined as the smallest target, capable of selective biologic reactivity.

(II) **Each reacton can give only one kind of response.** The nature of this response depends upon the inherent structure of the reacton itself. Hence, at the level of these ultimate units, reaction patterns can not yet be separated into the specific and the nonspecific. In other words, the concepts of quality and specificity of response have no meaning here.

(III) **Specificity of action depends upon the degree of selective affinity,** which an agent exhibits for certain reactons.

(IV) **Specificity of response depends upon the degree of freedom with which certain reactons can be activated** independently of others.

(V) **Intensity of response depends upon the number of reactons activated.** It is still to be determined whether the degree of activation has any importance at this fundamental level, or whether reactons are subject only to the "triggering" type of yes or no response, which necessarily leads to the complete discharge of the accumulated action-potential.

(VI) **Homotropic adaptation depends upon further work hypertrophy (and/or hyperplasia) of certain previously developed reactons.**

(VII) **Heterotropic "transadaptation" depends upon work hypertrophy (and/or hyperplasia) of certain undeveloped reactons at the expense of inactivity atrophy in others, which were previously developed.** It is this type of response that we have been accustomed to regard as a "qualitative" change. The schematic drawings (figures 4 and 5) help to illustrate these thoughts by a simple, mechanical analogy.

At first sight, it may be difficult to comprehend how simple quantitative responses, in a limited number of reactons, might give the virtually unlimited number of, qualitatively distinct, reaction patterns of which living matter is capable. Yet, it must be remembered that this is not without precedent in biology.

For instance, according to the Young-Helmholtz theory of vision, there are only three fundamental color sensations, red, green, and violet. By suitable combinations of these, all other colors can be formed. To explain this, it was assumed that there exist three kinds of nerve elements in the retina, each of which is specifically responsive to the stimulus of waves of a certain frequency, corresponding to one color. If the nerve elements corresponding to red and green were simultaneously set in action, the resulting sensation would be orange or yellow; if mainly the green and violet, the sensation would be blue or indigo, et cetera. Actually, no such nerve fibers or elements are known, but the theory is equally valid if the stimuli affect three photochemical substance-units. The innumerable melodies which can be derived from the simple keyboard of a piano (although each key can produce only one tone) have already been mentioned as another suitable analogy.

It is not too difficult to imagine that the many reaction-patterns of which any cell is capable could thus be "synthetized" by simple yes or no responses of its constituent reactons. In all these instances, the quality of the true fundamental element (as the pure color or pure tone) is invariable. Differences in kind cannot occur at the level of the elements; the impression of a qualitative change is created by blending the responses of the unchanging fundamental units.

The reacton hypothesis suggests experiments to test the feasibility of an *analysis and synthesis of cellular disease.*

If the concept is valid it should be possible to identify, by their characteristic actions upon the cell, common elements of activity ("actons") in various complex pathogens (microbes, drugs, rays, etc.) each affecting one type of reacton preferentially. (In chemistry, this would be comparable to the acidity [or the oxidizing power] of various molecules, which affect cognate receptive groups of various materials in essentially the same manner, and to a large extent, irrespectively of the other characteristics of the acid [or the oxidizing] molecule.)

Conversely, it should be possible to synthesize cellular disease by the application

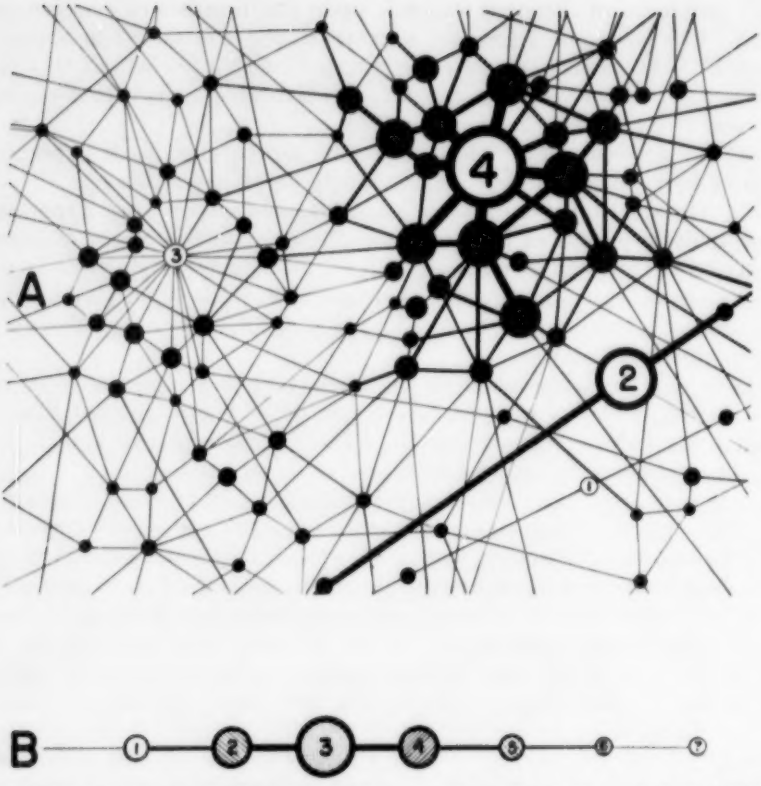


FIG. 4. **Schematic drawings illustrating the reacton hypothesis, as applied to the interpretation of specific and nonspecific actions.** In all these drawings, the individual reactons are schematically represented by round bodies, and the connections between them (interactions) by straight lines. This is similar to the customary representation of atoms and valences, respectively, in chemical formulae. Although, actually, reactons are arranged three dimensionally in living matter, they are shown here in a single plane, for simplicity's sake. The reactons, representatives of special conditions, are numbered.

A. *A field, containing numerous reactons (dots) in various stages of development ("surface view").* They are associated with each other by interactions of varying importance (straight lines). Thus, one might visualize them as the focal knots in a complex network of more or less obligatory or rigid interactions. Evidently, pressure exerted upon any focus will displace others as well; the extent to which local tension can spread will depend upon the number and strength of the connections between the directly affected focus and the rest of the system.

(1) Undeveloped reacton, directly connected only with two others.
(2) Highly developed reacton, directly connected only with two others.
(3) Undeveloped reacton, directly connected with many others.
(4) Highly developed reacton, connected with many others.

This illustrates that stimulation at a point, such as "1," will have a selective, specific effect (illustrated by "2"), while stimulation at a point, such as "3," will have a very generalized, rather nonspecific effect, even though the agent acted at one point only (illustrated by "4").

B. *Resting reactons.* Sample of seven reactons, not exposed to any agent ("profile view"). One (no. 3) is most developed and the prominence of the others diminishes as we approach the periphery of the former's activity range. This is intended to be a graphic expression of a situation in which (due to genetic factors or previous activity) even at rest, one type of reacton is most developed, while the others have evolved only in proportion to the importance of their interactions with the former. (E.g., in a developed muscle, the reactons directly and more or less indirectly related to contractility.) (After Selye;[6,7] Selye and Horava[4])

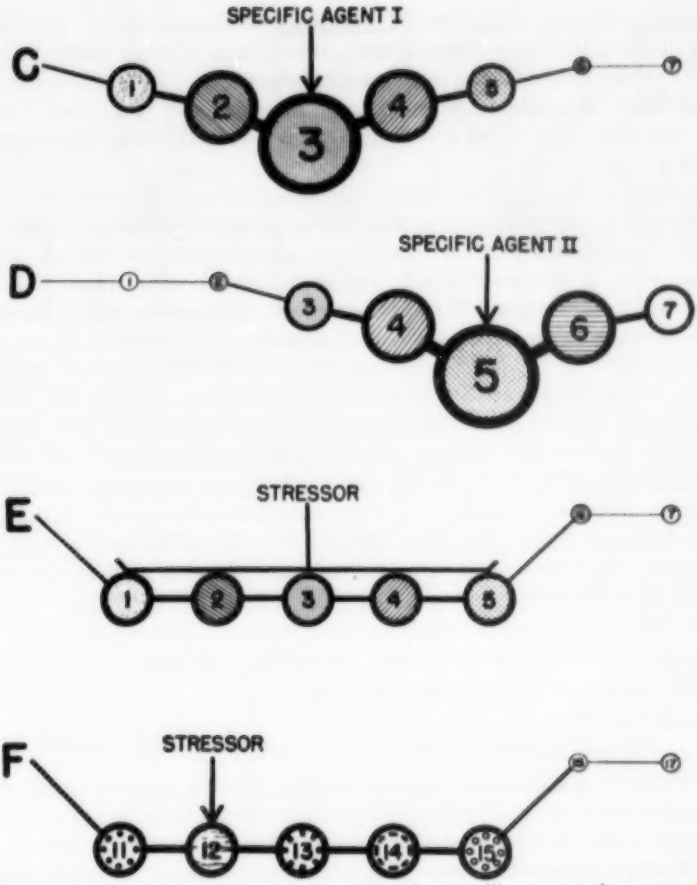


FIG. 5. **C.** *Specific effect with homotropic adaptation.* "Specific agent I" acts upon the system represented in "B," stimulating it to perform the function for which it has already been specialized. This leads to "simple work-hypertrophy" with a proportionate development of all the pertinent reactons and of their interactions. (E.g., in the above-mentioned example of the muscle, the repeated specific stimulation, through its motor nerve.)

D. *Specific effect with heterotropic adaptation.* "Specific agent II" calls upon the system represented in "B" to perform a function qualitatively different from that for which it had been specialized. Now, the chief emphasis is upon a previously not fully developed reacton (no. 5). This leads to a shift with varying degrees of "inactivity atrophy" in previously developed reactons (near the left end of the chain) and a corresponding "qualitative change" in structure and function. (E.g., selective exposure of a single muscle group to heat, with resulting dedifferentiation of the myocytes into polynuclear giant cells, suitable for the removal of damaged muscle cell debris.)

E. *Stress due to nonspecific action.* Here, the nature of the stressor is such that it affects all reactons and their interactions. The corresponding "dedifferentiation" is illustrated by a hypertrophy of the previously underdeveloped, at the expense of involution in the previously most developed, reactons. (E.g., exposure of a large tissue-area to heat, which directly affects all its cells.)

F. *Stress due to nonspecific reaction.* This also affects all reactons (and their bonds) in this field, although the stressor acts selectively on one (no. 12) alone. The reason for the generalization of the stress effect is the intense dependence of the units (nos. 11–15) upon each other, in this particular field. Thus, the response of one (no. 12) immediately produces marked repercussions in all others within the system. (E.g., overstimulation of the adrenal nerves, whose direct effect is highly specific, but the resulting adrenaline discharge produces a widespread stress response.) (After Selye,[6, 7] Selye and Horava[8])

—in suitable order and intensity—of several agents containing the requisite combination of elementary pathogens (actons), even if none of these agents be endowed in itself with the whole desired pathogenic combination. (To take another analogy from chemistry, this would correspond to the synthesis of NaCl from NaOH and HCl or from other salts of Na and Cl, none of which exhibits the characteristics of table salt.)

The greatest weakness of the reacton hypothesis is that, at present, we possess no criteria which would permit us to ascribe any elementary change within the cell (e.g., the accumulation of certain granules) to a single reacton. Since the latter can be defined only as the smallest unit capable of selective reactivity, it is always possible that further research will reveal further subdivisions within the observed objective indicator (e.g., the granule). However, this difficulty of spacially delimiting the individual reactons does not detract from the immediate practical applicability of the hypothesis, in the aforementioned sense. Even if now we cannot yet distinguish individual reactons from groups of reactons, the concept opens to experimental analysis that range of units between the cell and the chemical element.

Two analogies will help to illustrate our thought. It is of heuristic value to recognize that the color of an organ is not due to diffuse staining but to the selective accumulation of pigment granules in some of its cells. Observations made on this basis are not invalidated if it turns out subsequently that each granule contains several kinds of pigments.

It was of heuristic value to recognize that separate genes and not vague diffuse characteristics of living matter transmit inheritable characteristics much before the nature of the genes could be clearly delimited.

APOLOGIA OF TELEOLOGIC THOUGHT IN BIOLOGY AND MEDICINE

It is evident that our whole unifying concept is based upon teleologic thought, that is the principle of purposeful causality. It is difficult to understand why, among representatives of the exact sciences, and even among biologists and physicians, there is so much resistance to the use of teleologic arguments. Still we must admit that many of the most outstanding investigators of our time believe that one can —and indeed should—merely register scientific observations, refraining from all considerations of causality. I cannot follow such arguments. To my mind the sensation of causality is inherent in the structure of the human brain. Understanding itself is but the feeling of having securely attached a thing to our treasury of known facts, by solid bonds of obligatory sequences.

Knowledge includes purely descriptive information (the answer to: "What is it like?"), but we can "understand" only the cause of a thing (the answer to "What brings it about?"). In other words, we can know a thing by its characteristics (e.g., a house) or by the instinct of self-evidence (e.g., $6 \times 6 = 36$), but we can understand it only in terms of its cause.*

* In conversational English, the two terms are somewhat loosely used. For instance, we say that we "understand" a foreign word, but what we actually mean is that we know its meaning. This is really mere recognition by characteristics, and essentially different from true causal understanding.

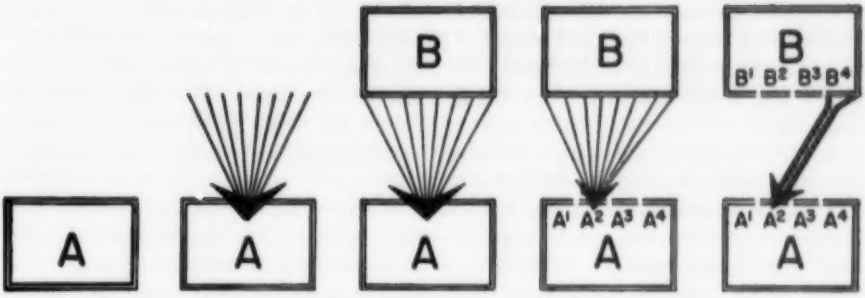


FIG. 6. **Diagram illustrating the usual sequence in problematology as we attempt to approximate the understanding of primary causes and primary elements in experimental medicine.** (Read from left to right) **(1.)** We discover a biologic target (e.g., the adrenal). This gives us knowledge, but not understanding. **(2.)** We notice that the target can vary, it is capable of being changed by agents of meanwhile unidentified nature and origin (e.g., adrenal enlargement). This gives us more knowledge, but still no real understanding. We ask ourselves "What is the cause of this change?" **(3.)** We find that the cause is "B" (e.g., the hypophysis). This gives us the impression that we understand the cause of the change. **(4.)** However, we soon find that the apparent change of the whole is actually due to an alteration of only one of its elements "A^2" (e.g., the adrenal cortex). Actually "B" acts on "A^2." **(5.)** Then we learn that not the whole of "B" but only "B^4" is the cause of the change (e.g., ACTH). Thus arises the sensation of an increasingly better understanding. It is not a coincidence that, as understanding deepens, the sequence of causality becomes increasingly more obligatory. "B" does not always act on "A" but only if it can reach "A^2." The response is still more predictable if "B^4" can be applied in abundance, since actually no other element of "B" is effective. The same argument applies to primary causes, when we begin to ask "What acts on 'B'?" (After Selye;[5-7] Selye and Horava[4])

This could be illustrated by figure 6.

But teleologic thought implies more than mere causality. It suggests an aim, that is purposeful causation. It is really because of this aspect that so many biologists refuse to accept it. As applied to our topic, the problem is rather clearly exemplified, for instance, in Schwartz's[9] recent monograph on inflammation. He states:

"One should think that the exalted Law of Nature—to vary a famous saying of Anatole France—recognizes no difference between microbes and man. One cannot consider inflammation as a specific 'cleansing' measure, that is one for the conservation of tissues, any more than one can envisage malignant neoplasia as having the 'purpose' or 'duty' to destroy organs: both processes are—just as all manifestations of Nature—*in themselves* aimless and purposeless phenomena."

We certainly could not avoid dealing with this problem in our discussion on stress. All our factual observations were arrived at through experiments planned on the assumption that stress responses are purposeful homeostatic reactions. We must realize that in both of the above-mentioned examples, there are two "teleologic centers;" their interests are opposed, but within each of them purposeful activity "for its own good" is clearly recognizable. On the one hand is the interest of the patient, on the other that of the microbe or the neoplastic growth. Indeed, the very essence of infection or neoplasia is the setting up of a center whose own interests are largely opposed to those of its host.

Of course, centers of homeostasis can exist within other such centers and, as soon as that is so, their interests will not be identical in every respect. To cite an example, a citizen shares many interests with all his countrymen, but, in ascend-

ing order, he shares even more with all those who live in the same city, or the same house. Not only bacteria and tumors, but even our normal tissues constantly compete with each other (e.g., for space or blood); hence, every cell, indeed every reacton within the body, represents a teleologic center whose purposeful reactions must be analyzed in relation to all other centers. Indeed the terms "teleology" and "purpose" can be meaningful only in relation to an identifiable center. "It is advantageous" means nothing unless we say for whom.

Actually, the formation of what might be called "teleologic centers" within the Universe appears to be one of the great laws of Nature. The stability of the most diverse structures appears to increase up to a certain optimum size or degree of complexity. The acquisition of this stability strikes us as an aim, since everything tends towards it. After they reached their optimal complexity, all structures tend to become unstable and "die" by falling apart, so that their elements may initiate another similar cycle. In its product, it is rare to find exactly the same elements, arranged in the same manner as in the parent structure, because precisely the same conditions are not likely to prevail twice in succession. This leads to a constant slow evolution towards more and more stable structures.

We see this in the case of small drops of mercury which, upon contact, tend to aggregate into a larger, more stable drop. This goes on until a certain optimal dimension is reached, then the drop becomes unstable, because of its size, and falls apart. We see this when a crystal develops, or an icicle, or an amoeba, or a human being. They only grow and fall apart in different ways. There can be simple shattering or disintegration (crystal, icicle), which makes all parts immediately available for totally different constructions. There can be direct and complete division into smaller structures, similar to the parent body (amoeba). In this case, there is no "corpse" from which to construct something totally new. And finally, an aggregate can fall apart by a combination of the two mechanisms (man) where a large part of the body disintegrates totally, yielding up its units (the "corpse") for wholly different constructions, while another part, the germ cell, is preserved for reproducing similar offspring.

Everything that persists for any length of time—that is, everything with any degree of stability—acts as a teleologic center in this sense. For this persistent activity it does not need the continued directing influence of an intelligent external influence with a purpose. Even a man-made object, once finished—an automobile, for instance—will give us the impression of continually looking out for its own interests; it will meet hostile influences with "intelligently planned defense reactions." When driven along the road, it will cool its own motor to prevent it from becoming damaged by heat. It will protect its body against shock with the aid of the springs, and, indeed nowadays, if it has self-sealing tires, it will even be capable of true "wound-healing" if punctured.

Of course someone has to make the automobile, and someone has to make the maker of the automobile, and this leads up to the point where our teleologically constructed brain can no longer follow, for we cannot understand anything without a cause.

We sense a Creator mainly because we and our surroundings strike us as being

"complex," and, during the short life-span of man, he sees no really complex structure being built up by chance, without the catalytic influence of a Maker. Why doubt, however, that in the span of ages, the organizing effect of a centralizing teleology could eventually build up awe-inspiring complexities, such as a planet, a tree, or even ourselves?

Having been built and being capable of building are the most immanent characteristics of our every part. Hence, we see everything through an atmosphere of building which tinges all our perceptions, just as a red crystal-ball, were it "alive" and capable of perceptions, would probably see everything as red, in and outside it. Teleologic thought does not necessarily have to lean upon a purposeful Creator, nor should it do so, even on religious grounds, since faith should not need the support of understanding. What we must clearly realize in biology is that teleologic analysis is applicable to any unit of creation, even after it is made.

Science cannot and should not attempt to embrace the purpose of the original Creator, but it can and constantly must examine teleologic motives in the objects of creation, since only this can lead to understanding, as opposed to a mere accumulation of unintelligible facts.

BIBLIOGRAPHY

1. Selye, H.: Stress: The Physiology and Pathology of Exposure to Stress, Acta, Inc., Medical Pub. Montreal, 1950.
2. Selye, H.: First Annual Report on Stress, Acta, Inc., Medical Pub. Montreal, 1951.
3. Selye, H., and Horava, A.: Second Annual Report on Stress, Acta, Inc., Medical Pub. Montreal, 1952.
4. Selye, H., and Horava, A.: Third Annual Report on Stress, Acta, Inc., Medical Pub. Montreal, 1953.
5. Selye, H.: The Story of the Adaptation Syndrome, Acta, Inc., Medical Pub. Montreal, 1952.
6. Selye, H.: The role of stress in health and disease, Explorations. *1*:57, 1953.
7. Selye, H.: On the nature of disease, Meyer Bodansky Lecture in Texas Rep. Biol. & Med. In press, 1954.
8. Barany, R.: Neurologisch interessante Resultate und Fragestellungen hervorgegangen aus Untersuchungen ueber aseptische Entzündung beim Menschen, Acta psychiat. et neurol. *8*:205, 1933.
9. Schwartz, P.: Entzündung Entzündungsbereitschaft und Immunität. Eine morphologisch-pathogenetische Stüdie, Springer Verlag. Wien, 1953.

about the author

Doctor Hans Selye was born in 1907 in Vienna, Austria. At the age of 17, he enrolled as a medical student at the German University of Prague. He also studied medicine at the University of Paris and at the University of Rome. He received his medical degree in 1929 from the German University of Prague, and he immediately began studies for his Doctor of Philosophy degree, which he received from the same university in 1931. He served as an assistant in experimental pathology at the German University of Prague from 1929 to 1931.

In 1931, Dr. Selye was awarded a Rockefeller research fellowship which he used

for study first at Johns Hopkins University (Department of Biochemical Hygiene) and then at McGill University (Department of Biochemistry). He remained at McGill in the following positions until 1945: 1933 to 1934, Lecturer in Biochemistry; 1934 to 1937, Assistant Professor of Biochemistry; 1937 to 1941, Assistant Professor of Histology; and from 1941 to 1945, Associate Professor of Histology. In 1945, Dr. Selye became Professor and Director of the Institute of Experimental Medicine and Surgery at the University of Montreal, and in the meantime, he had become a citizen of Canada. He has also served as an Expert Consultant to the Surgeon General, United States Army.

DR. HANS SELYE

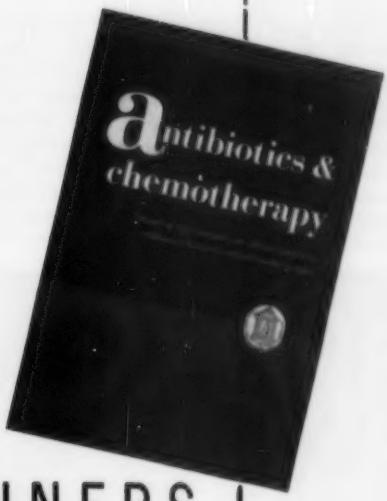
Since 1936, Dr. Selye, who now has 40 assistants, has been performing his investigations on stress. In recent years, Dr. Selye has made tremendous strides in discovering treatments for stress-caused diseases.

Recognized as one of the most outstanding endocrinologists alive today, Dr. Selye completed, after 15 years' work, a six-volume *Encyclopedia of Endocrinology*. He is the author of the following books: *Stress*, *The Physiology and Pathology of Exposure to Stress* (1950), *First Annual Report on Stress* (1951), *Second Annual Report on Stress* (1952, in collaboration with A. Horava), *Third Annual Report on Stress* (1953, in collaboration with Horava), *The Story of the Adaption Syndrome* (1952), *Textbook of Endocrinology*, 2nd edition (1949), and innumerable other works. Dr. Selye has also written over 400 scientific papers.

Dr. Selye is an active member of several scientific and medical societies in various countries throughout the world. He is an honorary member of the following societies: Aesculapian Society of the University of Ottawa (Canada), Russian Endocrinological Society (U.S.S.R.), Sociedad Argentina de Biologia (Argentina), Sociedad de Biologia (Chile), Sociedad Médico Quirurgica del Guayas (Ecuador), Sociedade de Endocrinologia e Metabologia de Rio de Janeiro (Brazil), Societas Endocrinologica Bohemica (Czechoslovakia), Svenska Endokrinologföreningen (Sweden), and many others.

Doctor Selye has been awarded the Medal of the Accademia Medico (1950) Fiorentina, Italy; the Heberden Research Medal (1950) London, England; Gordon Wilson Medal (1948) awarded by the American Clinical and Climatological Association; and Casgrain and Charbonneau Prize for original work leading to improvement in the prevention or treatment of disease.

6



NOBEL PRIZE WINNERS

E. CHAIN
SIR ALEXANDER FLEMING
SIR HOWARD W. FLOREY
BERNARDO A. HOUSSAY
E. C. KENDALL
SELMAN A. WAKSMAN

AMONG THE
75 DISTINGUISHED MEMBERS
ON THE EDITORIAL BOARD
OF
ANTIBIOTICS AND CHEMOTHERAPY

HENRY WELCH, Editor-in-Chief

Monthly Reports on Research and Clinical Application of Antibiotics, Hormones, Steroids, and other Biochemicals
Subscription Rates: One Year — $15.00 — Three Years — $39.00
Published Monthly by MD PUBLICATIONS, INC.
Editorial Offices: 30 East 60th Street, New York 22, N. Y.

Dr. Winfred Overholser Honored With Award

It is our great pleasure to announce that Winfred Overholser, M.D., Superintendent of St. Elizabeths Hospital (Washington, D. C.) and Editor in Chief of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY, was a recipient of the Distinguished Service Award, Gold Medal. This Award, which was presented to Dr. Overholser by the Department of Health, Education, and Welfare at the Annual Honor Awards Ceremony in Washington, D. C., on April 9, is the highest honor which the Department can bestow. At the Ceremony, only four Distinguished Service Awards were given, and Dr. Overholser received the award specifically "in recognition of his outstanding contributions to humanity in the field of mental health." Doctor Overholser's record illustrates that he has dedicated himself to the practice and fulfillment of the highest principles of his profession, and he deserves to be honored for his contributions toward the betterment of society.

DR. WINFRED OVERHOLSER

Doctor Overholser was born in Worcester, Massachusetts, April 12, 1892. He received the degree of Bachelor of Arts, Cum Laude, from Harvard University in 1912, and the degree of Doctor of Medicine from Boston University in 1916. In 1940, he was granted the honorary degree of Doctor of Science by Boston University. Following his period as resident physician at the Evans Memorial Hospital in Boston, he entered the Massachusetts State Hospital Service, remaining in that from 1917 to 1936. During that period, he was absent on military leave from February, 1918, to June, 1919, serving in the United States and France as a psychiatrist in the Medical Corps of the United States Army.

While in the Massachusetts State Hospital Service, he was on the staff of several institutions, and in 1924 he became Assistant to the Commissioner of Mental Diseases of the State. He was director of the division for the examination of prisoners of the Department of Mental Diseases of the Commonwealth of Massachusetts from 1925 to 1930, Assistant Commissioner from 1930 to 1934, and Commissioner of Mental Diseases from 1934 to December, 1936. In October, 1937, he became the Superintendent of Saint Elizabeths Hospital, which is a federal psychiatric institution. Under Doctor Overholser's knowledgeable guidance and unique leadership, St. Elizabeths has grown to be one of the best public mental hospitals in the United States. It is the only such hospital fully accredited by the American Medical Association for rotating internships.

Doctor Overholser is also well known in the teaching profession. He has had long experience in this field and was on the faculty of the Boston University Medical School from 1925 to 1934. Since 1938, he has been Professor of Psychiatry at the George Washington University School of Medicine.

During World War II, he served as Advisor to the Selective Service System and received the Selective Service Medal from the United States in recognition of his aid. He also served as Chairman of the Committee on Neuropsychiatry of the National Research Council. He has been prominent in numerous medical organizations and is a past president of the American Psychiatric Association. He is also a past president of the Academy of Medicine of Washington, D. C. He is a member of the Cosmos Club of Washington, D. C., and of the Sigma Xi, the honorary scientific fraternity. He is Chairman of the National Medical Advisory Board of the American Legion and a member of the National Board of Medical Examiners.

In August, 1948, Doctor Overholser was Chairman of United States Delegation to the International Congress of Mental Health, London, and in 1950, Vice President of the World Congress of Psychiatry,

(continued on page 208)

Dr. Henry Welch Cited For Distinguished Service

We are proud to report that Dr. Henry Welch, Director of the Antibiotics Division of the Food and Drug Administration and Editor of the journal ANTIBIOTICS AND CHEMOTHERAPY, was presented the Distinguished Service Award, Gold Medal, by the Department of Health, Education, and Welfare on April 9 at ceremonies in Washington, D. C. Doctor Welch, Editor in Chief of the journal ANTIBIOTICS AND CHEMOTHERAPY since its inception in 1950, has made this publication the most outstanding in its field. He believed in the clinical importance of antibiotics and realized the necessity for integrating in one Journal the many chemical, pharmacological, and medical reports on these drugs. ANTIBIOTICS AND CHEMOTHERAPY is recognized throughout the world as the most authoritative publication in the field of antibiotics.

The Distinguished Service Award is based on outstanding contributions to public health and science, as well as the demonstration of outstanding skill in public administration and distinguished authorship. Doctor Welch, who has devoted his life to the protection of public health, is more than worthy of this recognition of his tremendous achievements and of his loyalty to the finest ideals toward which man aspires.

DR. HENRY WELCH

Doctor Welch received his B.A. and M.S. degrees from Brown University and his Ph.D. degree from Western Reserve University. After obtaining his Doctorate in Philosophy, he became associated with the Connecticut State Health Department, where he worked as a research bacteriologist. He joined the Food and Drug Administration as a senior bacteriologist in 1938, and shortly thereafter his abilities not only as a brilliant research scientist, but as a leader and administrator were recognized. In 1943, when the United States Army requested that the Food and Drug Administration develop standards and methods for testing penicillin, Dr. Welch was entrusted with this responsibility. Even though there was not enough penicillin available at that time for experimental work, Dr. Welch, by developing a pilot plant and producing his own penicillin, evolved satisfactory methods for testing the potency and safety of this drug in a few short months. Since then the testing of antibiotics by the government has become an established procedure required by law, and Dr. Welch, through his genius for administration, has organized a highly trained team of scientific workers who test and certify the safety and efficacy of every batch of antibiotics distributed on the market today. On countless occasions, Dr. Welch has been commended by antibiotic producers for his efficient handling of the Division.

The program executed by Dr. Welch is magnitudinous in that his decisions affect millions of people not only in the United States, but in countries the world over. It is his responsibility to be sure that when the ultimate consumer receives an antibiotic the drug will have its full potency and will not be toxic. Dr. Welch has responded to the trust and responsibility invested in him with wisdom and judiciousness.

Other activities of Dr. Welch include the direction of a small research group that has published dozens of invaluable papers on antibiotics. Dr. Welch, a prolific writer, is the author of innumerable scientific articles, the coauthor (with Dr. Charles N. Lewis) of the book, *Antibiotic Therapy* (published by Medical Encyclopedia, Inc.) and a contributor of yearly chapters to *Diagnostic Procedures*, published by the American Public Health Association. He is also the editor of *Antibiotic Manual*, a handbook on antibiotics that includes a therapeutic index, a description of preparations, generic and trade names, and producers. It will be published in June, 1954, by Medical Encyclopedia, Inc. *Principles and Practice of Antibiotic Therapy*, written by Dr. Welch with sixteen coauthors, who are international authorities on antibiotics, will be published in May of this year, also by Medical Encyclopedia. The first half of this extraordinary and

timely book is a vivid history of the cyclonic evolution of antibiotics and a record of the experimental and research developments. In the second part of the book, the authors discuss the practical and applied uses of antibiotics in the various medical specialties.

Dr. Welch served as chairman of the Symposium on Antibiotics, which was organized and sponsored by the U. S. Department of Health, Education, and Welfare, Food and Drug Administration, in collaboration with the journal ANTIBIOTICS AND CHEMOTHERAPY. The Symposium was held in Washington, D. C., on October 28–30, 1953. A total of 102 scientific papers on antibiotics were presented at this Symposium by leading scientists of this country. Over 500 researchers and clinicians from the United States and abroad, attended the three-day meeting. The Symposium was so well organized that Dr. Welch was asked to make it an annual international event. The papers delivered at the Symposium were published in toto in the book *Antibiotics Annual: 1953–1954* under the editorship of Dr. Welch. Through his research, writings, lectures, and scientific publications, Dr. Welch has become an international authority in the field of antibiotics.

Henry Welch's contributions to humanity are truly immeasurable: his life is an example of constant devotion to science and mankind. We join our friends all over the world in congratulating Dr. Welch on the receiving of the Distinguished Service Award which he so richly deserves.

Dr. Winfred Overholser Honored With Award

(*Continued from page 206*)

Paris. He has been decorated by the French government as Chevalier of the Legion of Honor and by the Government of Ecuador with the Order "Al Merito." The Gold Key of American Congress of Physical Medicine was awarded to him in 1951 for work in occupational therapy and rehabilitation. First Isaac Ray Award of American Psychiatric Association was presented to him in 1952. He was again decorated by the French government in 1952, this time with the Medal of French Liberation. Gourgas Medal (Northern Masonic Jurisdiction, Scottish Rite Masons) was given to him in 1953.

As Editor in Chief of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY, Doctor Overholser has expanded the scope of the journal so that it is now one of the more comprehensive review publications. Doctor Overholser has also been a contributor to various legal and medical journals. He is the author of the book *Psychiatry and The Law* (1953) and *Handbook of Psychiatry* (with W. V. Richmond, 1947).

Doctor Winfred Overholser is more than worthy of the honor that was bestowed on him with the Distinguished Service Award. His many friends and colleagues here and abroad congratulate him on the winning of this well-earned award.

GENERAL PRACTICE CLINICS

Beginning with this issue, the General Practice Clinics section of the INTERNATIONAL RECORD OF MEDICINE introduces a new type of medical reporting that will be of interest to physicians everywhere. This section will now include comprehensive reports of papers delivered at current medical meetings in the United States and abroad. The following are specially prepared reports of speeches that were delivered before the Junior Faculty and Staff, Women's Medical College of Pennsylvania, Philadelphia; Southeast Branch, Philadelphia County Medical Society, Philadelphia; Medical Research Forum, New York Academy of Medicine, New York; Royal Society of Medicine, Section of Endocrinology, London, England, and the Philadelphia County Medical Society, Scientific Meeting, Philadelphia.

Certain Aspects of the Problem of Liver Cirrhosis

Presented by I. SNAPPER, M.D. (Beth-El Hospital, Brooklyn, New York) before the Junior Faculty and Staff, Women's Medical College of Pennsylvania, Philadelphia, February 17, 1954.

Liver cirrhosis must be carefully defined. There is one major criterion for cirrhosis: the architecture of the lobule must be destroyed. The presence of some fibrous tissue between intact lobules does not prove the presence of cirrhosis. The author recognizes four main types of cirrhosis: Laennec's (the most frequent), biliary, cholangiolitic, and toxic or postnecrotic cirrhosis.

In Laennec's cirrhosis the liver is hobnailed—but only to the pathologist. These hobnails cannot be palpated during life. If a patient has a nodular liver on physical examination, then he hardly ever has Laennec's cirrhosis. Histologically, the architecture of the lobules is destroyed by proliferation of fibrous tissue. In addition fibrous septa are formed, connecting the vessels of the portal triangles with the central veins of the lobules. Since these fibrous septa carry vessels, blood flows immediately from the portal circulation to the hepatic veins without having been in contact with the liver cells. Hereby hundreds of thousands of microscopic shunts are created—an internal portocaval anastomosis or Eck's fistula. This is very important, because: (1) portal blood is not processed by the liver; (2) the lobule does not receive enough blood, anoxia develops and this leads to progressive fibrosis of the liver lobules. In this way a vicious circle is started: fibrosis leads to anoxia which in its turn leads to more fibrosis. This is one of the reasons why portal cirrhosis is an incurable disease, which grows worse and worse until death occurs; (3) blood circumvents the liver by way of collateral circulation, which originates because the portal fibrosis represents a barrier for the portal blood

flow. This can be shown by postmortem injection of blood into the portal vein. In cirrhosis very little of this blood leaves the liver via the hepatic veins, and by far the greater part passes through the collateral circulation. As a result the cirrhotic liver receives 85 per cent of its blood supply from the hepatic artery. The collateral circulation causes the dangerous esophageal varicosities. In addition, it is responsible for the overfilling of many other parts of the abdominal and thoracic venous circulation. There is, for instance, always dilatation of the veins of the abdominal wall. Frequently these dilated veins cannot be discovered by inspection alone; however, they can nearly always be picked up by infra-red photography.

Another common finding in cirrhosis is splenomegaly. This is usually assumed to be due to portal hypertension; however, this is only partly true. If in experimental animals the spleen is transplanted to the abdominal wall and thereby completely isolated from the portal circulation, splenomegaly still results if cirrhosis is induced. This splenomegaly is due to a reticular hyperplasia of the spleen. Himsworth believes that this is caused by dead liver cells releasing toxic substances into the circulation which stimulate the reticuloendothelial system.

Portal hypertension produces a hypertension in the azygos and hemiazygos veins, because part of the collateral circulation of the cirrhotic liver empties in the lumbar veins. The overfilled lumbar veins connect through the diaphragm with the azygos and the hemiazygos. This is considered to offer a convenient explanation of the occurrence in cirrhosis of right sided pleural effusions. If fluid is found in the left pleural cavity, then the effusion must be caused by another disease and not by cirrhosis.

Why do patients die from liver cirrhosis? An average of 50 per cent of the cirrhotic patients die in hepatic coma and half of these develop their coma after an esophageal hemorrhage. Another 25 per cent die of the hemorrhage itself without going into coma. Twenty-five per cent die of other causes—frequently duodenal ulcer, although no one seems to know the reason why patients with liver cirrhosis have a tendency to develop peptic ulcers.

Often a patient with liver cirrhosis enters the hospital with an acute abdomen. This is nearly always due to subserous intestinal abscesses. Due to the increased venous pressure in the intestinal wall, the intestine's defenses against bacteria in its lumen are broken-down and bacterial transmigration from the lumen to the subserosa takes place.

Cardiac cirrhosis is a name given to the fibrosis frequently found in the liver in congestive heart failure. However, in congestive heart failure, an actual cirrhosis which fits the above described criteria is very rare. Congestion of the spleen due to increased venous pressure causes the spleen to be enlarged at autopsy. It should be emphasized that such an enlarged spleen never becomes palpable. If a palpable spleen is present in congestive failure, one should look for another explanation (constrictive pericarditis, true Laennec's cirrhosis, subacute bacterial endocarditis, et cetera).

Hemochromatosis produces a true liver cirrhosis. This disease usually occurs in males and is quite rare in females. Hemochromatosis is due to an abnormally

rapid absorption of iron from the gastrointestinal tract. The fasting serum iron is very high. Human serum can bind only a certain amount of iron. In normal persons the iron binding capacity of the serum is not saturated; in hemochromatosis the serum is saturated with iron. Lately it has been shown that patients with hemochromatosis do quite well when the excess iron is removed by regular venesections. Women do not develop this disease because every month they lose blood during the menstruation. Women patients with hemochromatosis occasionally have been observed: all these patients had hypomenorrhea or amenorrhea.

In hemosiderosis, caused by numerous blood transfusions, iron has been deposited in all organs. This hemosiderosis can be easily distinguished from hemochromatosis by bone marrow studies: there is no free iron in the bone marrow in hemochromatosis, while in hemosiderosis the marrow is full of iron.

Liver function tests must be used with common sense. Cephalin flocculation, thymol turbidity, and alkaline phosphatase are the ones commonly used. A positive cephalin flocculation test, if repeated several times, indicates degenerative disease of the liver. The reverse however is not true: a negative test does not exclude degenerative disease of the liver. Increase of the alkaline phosphatase of the serum should also be critically evaluated. In extrahepatic obstruction the alkaline phosphatase content of the serum is always increased. A high alkaline phosphatase of the serum however does not prove obstruction of the large extrahepatic ducts. On the other hand, a normal alkaline phosphatase practically excludes obstruction. Therefore, only the positive cephalin flocculation test and the normal alkaline phosphatase content of the serum have important diagnostic implications.

The level of the alkaline phosphatase in the blood is determined by the condition of the bones (since the osteoblasts produce alkaline phosphatase) and the condition of the bile flow. Even when the skeleton is normal, regurgitation of the alkaline phosphatase from the bile into the blood stream, caused by obstruction, is not the only reason why a high level of alkaline phosphatase is found. Liver disease without clearcut obstruction of the bile flow may also cause an increase in the alkaline phosphatase. Alkaline phosphatase is made in the walls of the small bile ducts. When these small cholangioles increase in number as happens during regeneration of liver tissue, the blood alkaline phosphatase goes up too. Thus in obstructive jaundice the high alkaline phosphatase is partly due to backflow of the bile, partly to proliferation of bile ducts.

The gamma globulin is produced by the Kupffer cells. Since the latter proliferate in liver cirrhosis, the gamma globulin content of the serum increases concomitantly.

Because so much blood is shunted past the liver cells in liver cirrhosis, the functions of the liver are damaged. In general, it can be said that the liver function tests do not examine the vitally important functions of the liver. Detoxication of poisonous substances by the liver cells is necessary for life, because potent poisons, e.g., indol, skatol, and phenol, are formed in the intestinal tract. These substances are much more toxic when injected into a peripheral vein than into the portal circulation, because they are detoxified by the liver by conjugation with sulfates and glucuronic acid. In hemochromatosis and in liver cirrhosis, the results of

deficient detoxication can be demonstrated in the form of signs of feminization. Males produce not only androgenic substances, but also female hormones. Under normal conditions these estrogenic substances are conjugated in the liver with glucuronic acid. Glucuronides of estrogens have no hormonal activities anymore. In cirrhosis, the conjugation of the estrogens does not take place in the diseased liver, and due to the excess of free estrogens, the male cirrhotic has a tendency to lose part of his male characteristics and to develop certain female traits, e.g., small testes, sparse pubic and axillary hair, gynecomastia, loss of libido, spider angiomas, liver palms. The two latter signs are due to the dilating effect of estrogens on the veins.

In Laennec's cirrhosis fluid is poorly excreted. A normal person will excrete 1500 cc. of administered fluid in four hours; it takes a cirrhotic 24 hours to do this, allegedly because the antidiuretic factor of the pituitary is not conjugated with other substances in the cirrhotic liver and reaches the kidney in nonadulterated form.

Within the past decade it has been emphasized that patients with Laennec's cirrhosis do better on a high protein diet. This conclusion was based upon the fact that animals develop cirrhosis on protein poor diets and that cirrhosis is more frequent in areas where the intake of protein is low, such as in China. Since cirrhosis is caused by low protein diets, high protein diets should be good for cirrhosis. In a way this conclusion is correct. When destitutes with cirrhosis are given a high protein diet, they improve on it. In cirrhotic patients whose diet has been sufficient, high protein diet has little effect.

Some physicians have gone even further and have reasoned "because high protein diet is good for Laennec's cirrhosis, it should have a salutary effect in any liver disease." This is certainly not proved. There exists considerable doubt that high protein diets have any merit in the prevention or treatment of posthepatic liver cirrhosis. In North China, for example, where the diet is very low in protein, infectious hepatitis is a mild disease. There is almost no acute or subacute liver cirrhosis and posthepatic cirrhosis is rare.

Medical science and especially therapy always develop in sinusoidal curves. The Eck fistula dog can live only on a *low* protein diet. Meat in the diet kills him! That is because in the intestine ammonia is formed by putrefaction of meat. In the Eck fistula dogs the ammonia reaches the peripheral blood because it is shunted around the liver and the dogs develop ammonia poisoning. This fact, discovered in 1907, was forgotten, so that it could be rediscovered recently. Also in patients with a portocaval shunt, a high protein diet may be deleterious. Since in cirrhosis numerous microscopic portocaval shunts exist, high protein diets in liver cirrhosis may occasionally have an adverse effect by increasing the ammoniemia. Most modern authors realize this. They are afraid to break away from the accepted high protein treatment, and as a golden middle road they now advise to give a moderately high protein diet.

All this must be emphasized because the old thesis that ammonia plays a role in the causation of hepatic coma has been revived. If ammonia is given to a

patient with severe cirrhosis, he may develop the flapping tremor which is characteristic for hepatic coma. Sometimes actual coma may set in. It is unwise, therefore, to use in cirrhosis ammonia containing diuretics such as NH_4Cl, or cation-exchange resins which contain ammonia. A drug which could bind ammonia might have a favorable influence upon hepatic coma. One way that this can be done is by administering glutamic acid intravenously in large amounts of 10 grams. Glutamic acid can bind ammonia to form glutamine, and this may or may not be the reason why this amino acid can improve hepatic coma. In addition glutamic acid is the only amino acid which is metabolized in the brain.

Ascites in cirrhosis due (1) to portal hypertension, which cannot be treated medically, and (2) low serum albumin, which perhaps can be treated medically. High protein diets should be given with caution, for the reason cited above. Intravenous injections of salt-free, pure albumen seem appropriate, because this does not lead to ammonia formation. However, due to the colloid osmotic pressure of the albumen, for every 12.5 Gm. of albumen injected, 175 cc. of fluid are added to the circulating blood volume.

The increase of the circulating blood volume which sets in under influence of this treatment may lead to rupture of esophageal varicosities and to fatal hemorrhages. Thus injections of salt-free albumen have been relinquished for the treatment of Laennec's liver cirrhosis, although they may have a salutary influence in longstanding hepatitis and in the early stages of posthepatitic liver cirrhosis.

The Aminoacidurias

Presented by Maxwell Scarf, M.D., (Albert Einstein Medical Center, Southern Division, Philadelphia) before Southeast Branch, Philadelphia County Medical Society, February 16, 1954.

As proteins are ingested they are broken down by enzymatic activity into amino acids. Normally these amino acids are rapidly deaminated by the liver, most of the nitrogen thus released being converted to urea. The remaining portions of the amino acids are converted into tissue proteins, or serve as precursors for enzymes and hormones, or contribute to the energy needs of the body. The mechanism of deamination is exceedingly efficient so that the serum amino acid level is low. This small amount of amino acids is filtered through the glomeruli, but most of it is reabsorbed by the tubules, so that the quantity of amino acids reaching the urine is slight. Thus, of all the urinary nitrogen, about 85 per cent is due to urea, about 14 per cent to ammonia, and only 1 per cent to amino acids. In any individual the slight loss of amino acids in the urine is a remarkable constant, which is unaffected by the dietary intake of proteins. The essential amino acids are excreted even less than the nonessential.

Excess secretion of amino acids in the urine are due to the following: (1) Liver disease: this causes high blood levels of amino acids because of faulty deamination.

The tubules of the kidney, although healthy, are unable to cope with the reabsorptive load delivered to them. The more serious the liver disease the greater the aminoaciduria. It is important to remember that an aminoacidemia is present and that aminoaciduria is proportionate to it.

To some extent, other diseases, all having in common severe tissue loss, such as occurs in widespread dystrophies, extensive burns, severe hyperthyroidism, carcinomatosis, prolonged use of ACTH, also may be attended with raised blood levels of amino acids with a consequent loss of these substances in the urine.

None of these are primary acidurias but merely reflections of the underlying disease.

(2) Kidney disease: overt kidney disease, whether it be a nephrosis, pyelonephritis, wireloop lesions of disseminated lupus, etc., is another source of secondary aminoacidurias. Here, the diseased tubules cannot effectively reabsorb the normal amount of amino acids presented to them. There is no preceding aminoacidemia.

(3) The most interesting clinical group are the primary aminoacidurias, where no liver disease is present, no preceding aminoacidemia, and no ascertainable anatomic lesions in the kidney.

CYSTINURIA

Cystinuria is a condition in which, because of an inborn error of metabolism, cystine is excreted in excess. Normally about 100 to 150 mg. of cystine is found in the urine; in cystinuria the amount may be 1 Gm. or more. Its frequency in the past was not known since dependence was solely predicated on crystalluria or discovery of radio-opaque stones. With modern chemical and chromatographic technics, the frequency has been established to be about 1 in 260 individuals. Fortunately, only a small percentage of people with cystinuria develop stones. Cystine is a sulfur containing amino acid. The sulfur portion of a normal urine shows only 5 per cent of it to be due to cystine; in patients with this metabolic defect, however, about 55 per cent of the urinary sulfur is due to cystine.

Recent chromatographic studies have shown that arginine and lipine are also excreted in excess in cystinuria. Cystine is the most insoluble of these 3 amino acids in an acid urine and, therefore, precipitates most easily. The consensus of opinion is that there is a selective tubular reabsorptive defect for these 3 amino acids. Despite the lifelong and constant loss of 3 amino acids, patients with this disorder are clinically well, aside from tendency to stone formation.

CYSTINOSIS

In cystinosis there is a widespread deposition of cystine crystals in many tissues of the body, particularly in the reticuloendothelial system. They appear as white flecks studding the viscera. This extensive infiltration of the tissues seriously interferes with function and the disease is almost invariably fatal in infancy or childhood. The disorder is due to an enzymatic defect which prevents the body from properly eliminating cystine. Cystinuria is not a feature of this condition.

DE TONI FANCONI SYNDROME

This disorder is also due to an hereditary error of metabolism and is characterized by an excessive urinary secretion of many amino acids. Ten or more may be excreted. Along with the aminoaciduria are also other abnormalities. Glycosuria occurs, leading to wasting, acidosis, and attacks of hypoglycemia. Phosphaturia, with a variable calciuria, may lead to irreversible, vitamin D-resistant rickets, osteomalacia, dwarfing, and fractures. Potassuria may be responsible for hypokalemic episodes. Bicarbonate is also lost in excess. The peptiduria that is present is but another means of losing amino acids. Cystine is usually not excreted in excess, although it may be one of the 10 or more amino acids that are lost through the urine.

In a few cases, cystinosis, or cystine storage disease occurs; hence, some investigators equate the DeToni-Fanconi syndrome with cystinosis—the latter being considered a variant of the former.

Clinically, the infant with this syndrome does well for the first six months. Then anorexia, polyuria, glycosuria, dehydration, acidosis, and fever supervene: rickets and fractures appear. The intense metabolic disorganization leads to death in childhood in the vast majority of instances.

The occurrence of so many reabsorptive abnormalities, all thought to reside in the proximal tubule, suggests the possibility of a powerful enzymatic defect of a nonspecific nature, possibly absence of some phosphatase, as a common denominator. Absence of an alkaline phosphatase was actually demonstrated in the tubules of 2 patients.

Lately, it has been realized that some patients with this disorder do reach adulthood. Twelve such cases have been reported to date. Milkman's disease is thought to be a variant of this disease. In adults osteomalacia is dominant, while in children rickets is common. In a few patients healing of fractures and some subsidence of aminoaciduria have been reported with the use of Shohl's solution (citric acid—sodium citrate), potassium chloride, and huge doses of vitamin D.

PHENYLPYRUVIC OLIGOPHRENIA

In this disease there is a disturbed metabolism of the amino acid phenylalanine leading to excretion of this substance and its oxidation products, i.e., phenylpyruvic acid and phenylpyruvic lactic acid. Phenylalanine is very similar in structure to tyrosine and is, indeed, usually converted into tyrosine. The enzyme necessary for this conversion is absent in this disease. Here, too, recent chromatographic studies have shown that a few other amino acids also find their way into the urine in abnormal amounts. These are glycine, tyrosine, alanine, proline, and aspartic acid.

The significance of this metabolic disorder lies in the fact that it is invariably attended with mental disease, chiefly mental retardation. About 1 per cent of children in institutions for the feeble-minded have phenylpyruvic oligophrenia.

WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)

Wilson's disease consists of a combination of liver disease and extrapyramidal symptoms and signs, in association with a ring of browning-green pigment at the corneal margin known as the Kaiser-Fleisher ring.

The liver disease manifests itself in the same manner as any cirrhosis. The lenticular degeneration makes itself known through tremors, rigidities, dysphagia, and dysarthria. It is a disease in which males are affected twice as often as females, where consanguinity occurs in about one third of the cases, and which is hereditary in a recessive manner.

Two important biochemical aspects are present in this disease. One of these aspects concerns copper metabolism. The serum copper and serum copper oxidase are conspicuously lower than normal in all patients so studied. However, the tissue copper is high, especially in the liver and the brain. The urinary copper is also high. In ordinary cirrhosis urine copper may also be high, but the pattern of high urine copper and low serum copper is of great importance in the diagnosis of Wilson's disease.

The other biochemical abnormality discovered by Dexny-Brown and Uzman in 1948 is an intense and constant aminoaciduria. Many amino acids, sometimes all, are excreted in amounts that may exceed 25 times the normal.

The liver disease that is present cannot be the cause of the aminoaciduria, because (1) in many patients with portal cirrhosis, there is no aminoaciduria, certainly never such an intense outpouring of amino acids. (2) There is no preceding aminoacidemia, and (3) in siblings of patients with Wilson's disease, aminoaciduria is present prior to any clinical or laboratory recognition of hepatic disease. Actually, the reverse may be the case, the loss of amino acids depriving the liver of these important building blocks to preserve its own integrity.

Any unifying concept of Wilson's disease must explain both the aminoaciduria and the disturbed copper metabolism. At this time it is impossible to state where the primacy of the enzymatic disturbance lies. It is possible that the disease is due to profound enzymatic disturbance which permits loss of amino acids that are essential to the functional and structural integrity of the liver and basal ganglia. Apparently an enzymatic disturbance in copper metabolism is necessary for the production of the complete picture.

Cardiac Pain in Man: Blocking Effect of Ethyl Chloride Spray on the Angina of Ergonovine

Presented by ISIDORE STEIN, M.D., SEYMOUR H. RINZLER, M.D., HYMAN BAKST, M.D., JOSEPH WEINSTEIN, M.D., ROBERT GITTLER, M.D., AND JANET TRAVELL, M.D., before the Medical Research Forum, N. Y. Academy of Medicine, January 28, 1954.

Since 1944, the authors have been using ergonovine maleate intravenously as a therapeutic adjunct in the diagnosis of coronary insufficiency in those cases where

the electrocardiogram is normal and where the history may be slightly atypical. The ergonovine has been utilized in an attempt—when the test is successful—to produce pain, which is similar to that experienced by the patient on exertion, and characteristic electrocardiographic changes of coronary insufficiency. The pain and EKG changes promptly disappear following the administration of sublingual nitroglycerine.

In performing the test, 0.1 to 0.4 mg. of ergonovine maleate in 0.5 to 2 cc. of water is slowly injected intravenously in an attempt to see whether the aforementioned responses are elicited. In 90 controls so tested, no pain nor EKG changes were noted. In 90 patients who had effort angina and normal electrocardiographic tracings, the I.V. ergonovine test produced positive results in 76 of these patients. Seventy patients experienced both the pain and the EKG changes; 2 patients had the pain alone, and 4 patients showed only electrocardiographic changes. The whole process (both pain and EKG) was quickly reversible by nitroglycerine. The changes in blood pressure and pulse that were noted during the performance of the test were negligible.

In 7 of the patients with effort angina and positive EKG changes, various tests utilizing an ethyl chloride spray were done. If the area (or part of the area where the patient complained of pain on effort) was sprayed prior to the injection of ergonovine, all patients still had EKG changes after injection, but only 3 had pain in the sprayed area, while 4 experienced no pain where the ethyl chloride had been sprayed. When the ethyl chloride was sprayed on the pain areas after the ergonovine maleate had been injected, 4 patients had complete alleviation of pain in the spray site, 2 patients had partial subsidence of pain, and the remaining patient did not have definite results. In all cases, EKG changes persisted until nitroglycerine was taken and its effects produced.

The theory expressed as to the mechanism of obliteration of the artificially induced anginal pain, without alleviation of the EKG changes, was that of counter irritation.

From the primary part of their work, the authors concluded that the use of ergonovine maleate as a diagnostic aid in the diagnosis of questionable angina and coronary insufficiency is reliable and of value (84 per cent reliable in their series).

Practical Application of Endocrinology to Other Branches of Medicine: Illustrated by a Case of Male Hypogonadism

Presented by RAYMOND GREENE, M.D., (Royal Northern Hospital and New End Hospital, London) before the Royal Society of Medicine, Section of Endocrinology, London, January 27, 1954.

The patient, a tall, thin, eunuchoid man of 29, with disproportionate growth of the long bones and a bone age of 18 years, suffered from frequent slipping of the epiphyses with consequent effusion into his knee joints. Implantation of 1 Gm. of testosterone improved sexual development but had no effect on the epiphyses.

Two further implants totalling 1.5 Gm. testosterone and 600 mg. estradiol stopped upward growth at 6 feet 2 inches and increased the patient's weight from 146 pounds to 163 pounds.

Dr. Greene discussed the action of androgens and estrogens on bone growth and epiphyseal union, pointing out that pure androgens had a negligible influence on epiphyseal closure—contrary results reported by earlier investigators being due probably to contamination of androgens with estrogens. Oestrogens, on the other hand, cause rapid union of the epiphyses, and the patient in question suffered no further inconvenience from this cause after treatment with estradiol. The addition of testosterone prevented feminization and increased the weight and general masculinity of the patient.

Familial Hypogonadism

Presented by D. G. FERRIMAN, M.D., (North Middlesex Hospital, England) before the Royal Society of Medicine, Section on Endocrinology, London, January 27, 1954.

Hereditary forms of familial hypogonadism are unusual. Recessive and sex-linked forms of transmission present no difficulty; dominant forms are more difficult to explain. It is important to remember that there is *no* "all or none" law, and that some slightly affected people (less fertile) are a vital link which may not be detected or may be overlooked in the analysis. Apart from the clinical features, histology (e.g., testicular biopsy), hormone assay (e.g., excess gonadotrophin), and response to treatment have to be considered in the distinction between primary gonadal and primary pituitary syndromes.

There was presented a discussion of various families with dystrophia myotonica, Laurence-Moon-Biedl's syndrome, cryptorchidism, and Turner's syndrome (where dominant transmission and female predilection seems possible). A miscellaneous group was reviewed. Sporadic cases present a bewildering variety of pictures, and it is difficult to decide whether the varied pictures represent many separate diseases, or varying manifestations of a few. Careful study of the families of such cases is, however, worthwhile, interesting, and sometimes revealing.

Furadantin in the Treatment of Infections Due to Antibiotic Resistant Organisms

Presented by CHARLES E. FRIEDGOOD, M.D. AND CHARLES B. RIPSTEIN, M.D. (The Maimonides Hospital, Brooklyn, and the State University of New York College of Medicine, New York City) before the Medical Research Forum, N. Y. Academy of Medicine, January 28, 1954.

Work and results obtained on 200 patients (at this report) with antibiotic resistant infections, primarily of the urinary tract, indicate that Furadantin® is an effective addition to the antibiotic and chemotherapeutic armamentarium. Furadantin has been shown to be especially effective against the resistant *Bacillus*

proteus and other gram-negative organisms that have failed to be controlled by other antibiotics.

Work with rats showed that a wide margin of safety exists in doses comparably much greater than those used in man, with only mild testicular atrophy and some degeneration of the seminiferous tubules occurring, both phenomena being reversible in the rat with the cessation of therapy. The drug is found to be 40 per cent excreted in the urine and is therefore of value in urinary tract infections.

Two hundred patients have had Furadantin therapy at the Maimonides Hospital, of which 190 were treated for cystitis and pyelonephritis. All these patients had unsuccessful therapy previously with various antibiotics. Most of the infections were due to *B. proteus*.

The drug is administered orally in four divided doses, the daily dose being 5 to 10 mg. per Kg. of body weight. Among the varied laboratory tests done on these patients were urine cultures every three days in addition to sensitivity tests. Therapy was continued until all cultures were negative or there was a clinical relief in symptomatology, if the urine could not be sterilized. The term of therapy varied from 3 days to 3 weeks, with an average of 7 days. The patients ranged in age from 9 months to over 60 years. The average daily adult dose of the drug was 100 mg., four times a day, orally.

100 Cases of GU Infection-Results of Furadantin

	Cases	Clinical and Lab. Cure	Clinical Cure	Failures
Acute	42	33	8	1
Chronic	58	35	20	3
Total	100	68	28	4

Chronic cases in the above reported series were those that had experienced symptoms for over a month prior to the onset of therapy. Symptomatic relief was found predominantly in the chronic cases, especially where there was evidence of obstructive symptoms.

The authors had 6 cases of *B. proteus* septicemia that had been refractory to other therapies, and with Furadantin there were 5 cures with sterile blood cultures being obtained within 24 hours of the onset of therapy. In one case death occurred 8 hours after Furadantin therapy was started. With high doses of the drug, nausea and vomiting are occasionally experienced by the patients. Tests to determine liver and kidney function, and blood counts done during therapy showed no abnormalities that could be ascribed to Furadantin toxicity.

Furadantin has also been shown to have effect on resistant *B. coli*, Pseudomonas infections, and aerobacter aerogenes, as well as some resistant staphylococcal infections in man. Two cases of chronic intractable empyema, in which local application of Furadantin in powder form resulted in cure, were also reported.

Hearing Problems: Their Detection and Management

Presented by DAVID MYERS, M.D., (St. Christopher's Hospital) before the Philadelphia County Medical Society, Scientific Meeting, February 10, 1954.

The usual course of a deaf baby's early life is that the deafness is suspected by the mother at a rather early age, but she keeps it to herself, either in ignorance or in the hopes that the baby will outgrow it. The child usually doesn't outgrow it, and the advantage of early training is lost.

Some clues to diagnosing deafness early are: (1) slowness in learning to speak, not being able to hear, the baby cannot imitate; (2) failure to be comforted by soothing words spoken by the parent, as most babies usually are; (3) failure to identify parental footsteps and sounds; (4) appearance of a behavior problem.

Hearing tests for children are much different than those for adults. The author uses a set of Halloween noisemakers bought at the five and ten cent stores. These can be graduated in order of intensity, which is determined by usual means. The threshold of hearing for the child is the level of noise produced by the noisemaker that uniformly attracts his attention when sounded behind him.

Clinical observation is also very important. The author has observed that only 60 per cent of deaf children have true peripheral deafness. The other 40 per cent can be divided into three groups: (1) autistic, usually schizophrenic children; (2) mentally deficient children, and (3) children with brain injury leading to aphasia. These can usually be easily differentiated.

The child with true peripheral deafness is an alert child. He comes into the room and looks carefully around in order to orient himself visually, since he can't do so by ear. He is usually friendly and attractive, and smiles easily. He learns well, and often learns to lip read as early as two to three years of age.

The child with aphasia due to cerebral palsy can hear but can't use words. He is incapable of "inner" speech—of thinking in terms of words. His attention is hard to hold; he constantly picks up and puts down various objects. He enters the room and runs around it, touching things, and he is extremely curious, although his span of curiosity is short-lived.

The schizophrenic child is absorbed in himself and won't respond to external stimuli. He may hear very low-intensity stimuli at some times, and at others he will not even respond to touch. The mentally retarded child is usually obvious because of his lack of development in other facilities besides speech.

MEDICAL HUMANITIES

The Artist as Physician*

MEDICAL PHILOSOPHY IN THE RENAISSANCE

Félix Martí-Ibáñez, M.D.

NEW YORK, N. Y.

Renaissance science and medieval belief. The "time-axis" and the "visceral" countries. The Renaissance as a crisis. Purposes and orientation of Renaissance medicine. Art and medicine. Art in the Renaissance. The psychological meaning of Renaissance anatomic art. Anatomy among the Renaissance masters: The schools of Florence, Venice, Umbria: Verocchio, Botticelli, Piero Signorelli, Donatello, Raphael, Michelangelo. And—Leonardo.

If we had to decide what figures incarnated the greatest medical knowledge available at each period in the history of medicine, we should choose the seer for Mesopotamia, the priest and the philosopher for ancient Greece, the soldier for imperial Rome, the erudite monk and the alchemist for the Arabian and European Middle Ages, and for the Italian Renaissance—the artist and the humanist. Each one of these figures was the leader who provided new impetus for the medicine of his period.

Medicine in the Renaissance made three fundamental advances that paved the way for modern science: it undermined the authority of the old dogmatic Medicine, which crumbled like an ancient castle exhausted by the weight of centuries; it laid the scientific foundation for modern Anatomy; it made the decisive step forward in pharmaceutical Chemistry.

Of these revolutionary advances—personified in the iconoclastic genius of Paracelsus and the naturalistic thought of Vesalius—the most important is the contribution Vesalius made to Anatomy with his book, *De Humani Corporis Fabrica*, keystone of modern science. Vesalius' famous anatomic illustrations crystallized all that Renaissance artists had evolved before him.

The psychological and historical analysis of Renaissance art and culture will help us ferret out the secret of that amazing outburst of anatomic illustration underlying the Renaissance progress in medical sciences.

---

*"The Artist as Physician" is a chapter from *Centaur: A Biography of Medical Thought*, which is a work in progress by the author.

Most histories of medicine record medical ideas as emerging one from the other in logical and inevitable sequence. Human intelligence, however, does not function in this self-contained manner but is directed by the imperative needs of our life. Thought is a reaction to preintellectual human needs. Any given intellectual occupation is preceded by an emotional *pre*-occupation. Man does not concern himself with knowing simply because he is endowed with a mind. Underneath that generic knowledge called science, there is a vital function which inspires it: belief. And when man wavers between two beliefs without choosing one or the other, he is living through a historical crisis. That is what occurred in the Renaissance.

In the thirteenth century—apex of the fabulous period starting with Albertus Magnus and ending with Saint Thomas Aquinas—man pitched his tent in a world where he was guided by one single idea to which all the needles of the medieval compass pointed: the Divinity.

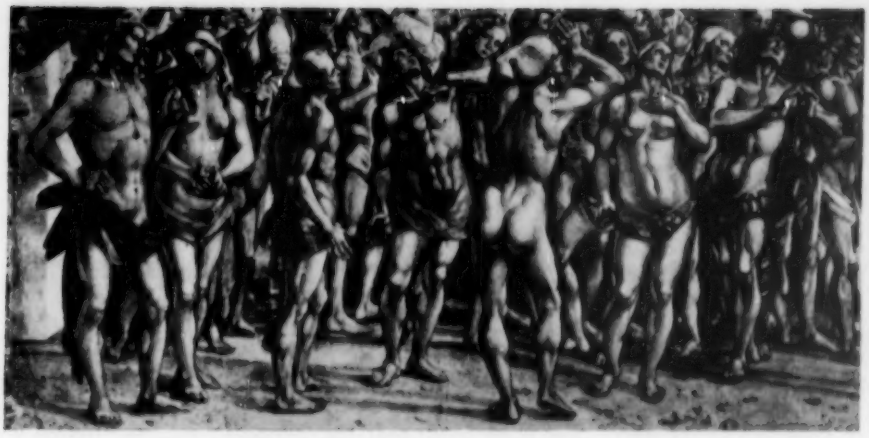
From the Crusades, the most extravagant adventures ever undertaken by human beings, Western man returned a military failure but faced a glorious future. For in his travels he established contact with an Arabic civilization impregnated with Greek culture, and when he returned home he brought, strapped on the back of his horse, the rich booty of Arabigo-Hellenic wisdom.

And so there fell upon warring Christian Europe—which was hardly intellectual and not one bit scientific—a shower of new knowledge fed by ancient Greek science and based therefore on pure reason. Instead of resisting Aristotelian science, Christianity accepted it and tried to assimilate the fruits of lucid Greek thinking. Albertus Magnus and Saint Thomas Aquinas, the two great medieval philosophers, polished the facets of the Christian diamond in the manner dictated by Greek ideology.

This was the second attempt, after Saint Augustine, to Hellenize Christian thought. The Christian *theos* united with the Greek *logos*; the result was a reform of medieval *theo-logy*. The gothic-evangelic inspiration of the Middle Ages was buried beneath the avalanche of Aristotelian *Corpus*. For the Greeks, courage and ingenuity were the keys to existence, just as for the Romans they were a militarized state and a regimented bureaucracy. The Asiatics, on the other hand, were content simply to live, guided by the hand of God.

During the Renaissance, the relation of man to God changed radically. In primitive societies, man was concerned with seeking a relationship with God; in the Renaissance, with Nature; whereas in our era man attempts to find his relationship with man.

When Constantinople and Byzantium fell into Turkish hands, Hellenic knowledge was transposed to the West in the form of Greek manuscripts hidden in the travel pouches of Byzantine scholars. Thus, the vast impetus of Hellenic humanism was set in motion. The word *humanist* became international and was synonymous with that cultural viewpoint that saw in man the measure of all things (the *Uomo*



Detail of a fresco by Luca Signorelli (circa 1450–1523) from the chapel of S. Brizio in Orvieto, Italy.

mensura of Protagoras). Humanism stimulated scholars to become reacquainted with true Latinity.

Renaissance man joyfully proved that the hoary classical clock of his Greek forbears could still mark the right time. The *humanities* began to challenge the *divinities*, although humanism also embraced religion and established—through Erasmus and Vives—a balance between God and man. In order to compensate for these ideologic and scientific complications, Renaissance man attempted to simplify existence by turning to classicism.

Paradoxically enough, the Renaissance begins as man takes a step backward and then makes the great jump forward. Man is determined to return to a simple culture and even to the stage preceding culture: he wishes to return to bare Nature. And as man throws off the heavy raiments of medieval philosophy, in that process of simplification which always characterizes despair, he is also ready to unclothe himself artistically.

Science becomes a wall between man and the symbolic medieval universe. Nature becomes a screen separating God from man. As man begins to predict the future course of cosmic and biologic events, he recovers his lost self-confidence and follows a new humanism, with his very own self as the starting point. From the fifth century, history had traced a Christian path along which man, pushed by despair towards religion and the next world, kept ascending until the thirteenth century, and then in the Renaissance plummeted back to the earth he had wished to leave behind. In the Quattrocento, the exhausted medieval skyrockets sputter down to earth while new ones soar above the horizon.

Renaissance man follows a dramatic pattern of life and requires vital tasks to occupy his attention. Although his faith is far less fervent than it had been, he still believes in a medieval God but feels a new confidence in himself and in his

world. To have faith, however, is quite different from having concrete knowledge. A historically demonstrable objective truth persists even without men of faith. In the Renaissance, *cognition*, or unlimited knowledge, and *sentire et scire*, or natural perception, replace faith and medieval scholasticism as basic elements of predominant thought patterns.

Enthusiasm over Nature, then, provided the impulse for the study of Nature. At first it was only a vague interest in natural things—partially resembling earlier mysticism—which encouraged demonology, astrology, magic, dream interpretation, and alchemy; but then came the desire for the methodical investigation of Nature that characterized neo-Platonism. Aristotelianism survived only as a speculative concept of Nature.

In the Middle Ages theology led science in the same manner that a totally blind man might lead a half-blind man. It is true that the thirteenth century was a flash of lightning in the dark. But if we recall that the fourteenth century brought a relapse into the darkness of earlier centuries, we see, along with Osler, that the thirteenth century was not the dawn that slowly turns into daylight, but an *aurora borealis* which flared up and then went down into the arctic night of medievalism.

THE TIME-AXIS AND THE "VISCERAL" COUNTRIES

In every period of History certain areas of the planet acquire a sudden staggering importance. This Karl Jaspers pointed out when he referred to that *time-axis* when China, India, and Greece became, circa 500 B.C., the spiritual axis of mankind. In every period of History there are certain countries that act as the vital organs of the world, while others remain on the periphery and are mere adipose tissue. In the fifteenth century, three nations stand out as focal organs whose rhythm provides the answer to the problems of that era: Italy, the Low Countries, and Spain.

At the beginning of the fifteenth century, Italy is the heart of Europe; it is the most advanced country intellectually and emotionally and is almost completely free of the mystical, ideologic circle of the Middle Ages; the Low Countries represent the greatest religious advancement; while Spain makes the greatest strides politically. In the Renaissance, the Low Countries plant the seeds of modern religion and Spain founds the modern State; but to Italy goes the glory of creating the *nuova scienza*.

The historic phenomenon of the Italian Renaissance is essentially Mediterranean. This sudden rebirth of classical ideas, this almost springlike resurrection, recurs periodically in Mediterranean history. Minoan culture was reborn in Periclean Athens. Hellenism reappeared in Alexandria and then again in the Renaissance. This historical rebirth always occurs around the Mediterranean for biological reasons, among them a propensity to emotionalism and a mental alertness created by paradisiacal climates and by the intermingling of a great number of civilizations. If

the history of medieval Europe is contained in the history of Spain, the heart beat of Italy synthesizes the history of the Renaissance.*

THE RENAISSANCE AS A CRISIS

The Renaissance represents a crisis. It is a rebirth. And to be *re*born is more important than to be born, for rebirth comes about with full awareness of the fact that one is going to live again. Resurrection has always moved men more deeply than birth itself.

Between the uncertainties of the Middle Ages and the all-embracing intellectualism of the seventeenth century, the Renaissance emerges in deep crisis. As man realized that his world was disintegrating, he fell victim to an uneasiness that lasted from 1400 to 1600. At the dawn of the seventeenth century, he finally found his place in a new world. Galileo and Descartes were his patron saints in the tremendous spiritual exodus.

Man, then, begins to live between the sword and the wall. Behind him he leaves a formulistic Christianity; before him rises a world which looks unalterable. The horizon is closed off on the side of the future. His only alternative is to return to the past philosophically and enjoy the present physically. Since a disintegrating tradition failed him and he foresaw only a confused, dark future, man had to turn inward, upon himself, upon his body, and to Nature as his last resources.

Many different factors were involved in this formidable growth of individualism and relaxation of authority: rationalism, freedom of thought and opinion, the circumnavigation of the globe by Spaniards and Portuguese and later by the English and Dutch, the discovery of the printing press which aided in the diffusion of culture (among the incunabula were works on popular medicine as well as the Bible), the discovery of gunpowder which destroyed feudalism, and the discovery of heliocentric astronomy by a Polish physician called Copernicus.

In Italy, the Renaissance begins in the XIV century with two poets: Dante, critic, historian, and political rebel, and Petrarch, who heralded a return to Nature and the classics. Italy, still recovering from pestilence and war, felt the need for new intellectual triumphs—a triumph over the constellations in the heavens, over the countries beyond the seas, over the secrets of the human body. Man replaces God Himself as the center of interest.

It is a portentous era. Great names rise in the horizon like new dawns. It is the era of Lorenzo the Magnificent and the House of Medici, of Ludovico il Moro and the House of Sforza, of Popes Julius II and Leo X, the Borgias—Rodrigo, Cesare, Lucrezia—, Machiavelli, Michelangelo, Savonarola, Castiglione, Cellini, Gutenberg, Henry VIII, Titian, Holbein, Erasmus, Dürer, Bramante, Pico della Mirandola, François Villon, Botticelli, Isabel and Ferdinand, Columbus, Torricelli, Pinturiccio, Calcar, Charles V, and Luther. It is the era of Raphael, El Greco, Cortés, Balboa,

* The center of gravity is then displaced. If ancient life was cosmocentric and medieval life theocentric, in the Renaissance modern life suddenly becomes anthropocentric. If at the beginning of the Renaissance the Gothic still predominates, such medieval thought has already become independent of God.

Pizarro, Magellan, Rabelais, Servetus, Cervantes, Lope de Vega, Shakespeare, Calvin, Saint Theresa, Saint Ignatius of Loyola, Tycho-Brahe, Galileo, Kepler, Cesalpino, Paré, Bacon and Copernicus. Leonardo. And Vesalius.

It is an era of palaces, glittering jewels, sumptuous velvets and silks, exquisite gold and silver work, magnificent weapons, proud statues, and gigantic cathedrals. It is the era of the Inquisition, of struggles between barons, popes, feudal lords, and *condottieri*. The class struggle had begun with the Magna Carta, but the struggle of faiths reached its height with the Reformation. It was a period that marked the foundation of universities run like democracies at Freiburg, Basel, Thuringia, Toledo, and Valencia. Granada was conquered and the Moors were expelled from Spain. And the Americas were discovered.

PURPOSES AND ORIENTATION OF RENAISSANCE MEDICINE

During this glorious rebirth of culture, the *leaders* of Medicine were the artists, who made the greatest contributions to Anatomy.

The renaissance of Medicine develops parallel with the *re*birth of the arts and literature. The new ideal of human and political individuality brings in its wake the study of the forms and functions of man. Illness ceases to be a divine punishment and becomes a derangement in the harmony of nature.

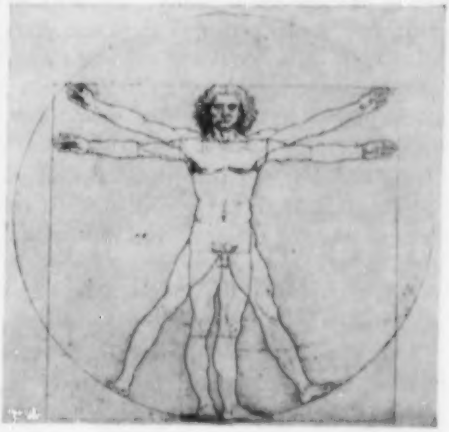
Medicine sprang originally from primitive terror of the unknown; it allied itself with magic and later with philosophy and religion; but in the Renaissance, medicine joined forces with art. The rigid, hieratical figures became more human, and anatomic drawings began to reveal the human body. The artist became an anatomist and the physician an artist, as in the cases of Berengarius and Fracastoro. For the new *uomo universalis*, who replaced the *uomo sanctus* and *uomo doctus* of former days, anatomy became the basis for the teaching of medicine.

A passion for exploration and the worship of antiquity are antagonistic forces in the Renaissance. But the *nuova scienza* wins the battle. In 1543 and 1546, three books, which were to become decisive in the history of scientific thought, appear: *De Humani Corporis Fabrica* by Vesalius, *De revolutionibus orbium coelestium* of Nicolaus Copernicus, and the *De contagioni et contagiosis morbis* of Girolamo Fracastoro. These three men had studied medicine at the University of Padua and were the standard-bearers in the struggle against the entrenched principles of Galen and Ptolemy. Before them, medical texts had been mere philosophic tracts, and teaching had been syllogistic and theoretical dialectic. But from Vesalius on, editions of the old Hippocratic and Galenic *Corpus* with commentaries spring up everywhere.

The Middle Ages, especially the thirteenth century, had been in a sense a period of splendor, when men built magnificent cathedrals with huge stained-glass windows through which the sun dressed the faithful kneeling in prayer in glittering polychrome rags. Dante, too, marked a high point in the history of the world. But if in theology the thirteenth century produced an incomparable trio—Abelard, Albertus Magnus, and Thomas Aquinas—in the field of medicine it produced nothing, and man remained enslaved to Greek and Arabic theories. The flame of medical knowledge, which the Arabs had kindled in Greek lamps and which

had shone without interruption from the eighth to the thirteenth centuries, was a flame that yielded no creative warmth.

In the Renaissance, interest in the classical world was revived when humanists like Linacre, Fracastoro, Gessner, and Caius, who were naturalists and botanists as well as physicians, rediscovered Greek philosophico-scientific thought and "with the New Testament in one hand and Aristotle in the other, resuscitated Greece" (Osler).



Leonardo's drawing of the proportions of the human body in accordance with mathematical laws after Vitruvius.

In addition, there was an awakening of interest in the anatomic structures of the human body, a movement spurred on by artists, like Leonardo, who had the mind of a physician, and physicians, like Vesalius, who had the soul of an artist. The printing press made the diffusion of classical texts possible, and anatomic illustrations replaced symbolic drawings.

If Renaissance architecture and painting were national, medicine, science, and the universities assumed an international character. In XVIth century Europe, the University of Padua, wisely governed by the Republic of Venice, protected freedom of thought, which was constantly persecuted in other universities. In Padua, astronomers, mathematicians, and physicians opened new vistas to the future. Copernicus prepared the way for Galileo, Vesalius for Harvey, Fracastoro for modern pathology. The XVIth century saw a revolution against the dogmatism of the medical classics—especially against the authority of Galen and Avicenna—which had kept physicians intellectually enslaved for over two thousand years. It was a real revolution with Paracelsus as leader. And in the XVIIth century, men gave meaning and function to the anatomic structures of the human body discovered in the Renaissance.*

---

* Before the Renaissance, Anatomy had had to struggle against obstacles put in its way by Religion. The history of the development of Anatomy is the history of the popular attitude towards dissection. Even in 1750 the prisoners of Newgate trembled at the possibility of their being used after death for anatomic research. When in 1820 a felon hanged at Carlisle was dissected, his friends attacked the physicians who performed the dissection.

It is true that Talmudic literature contains references to the dissection of dead slaves or those condemned to death by the Egyptian monarchs. Herophilus, the father of Anatomy, practiced vivisection in Alexandria, where Galen did his studies in osteology and myology. But then followed hundreds of years of paralysis in these fields. The two principal reasons for this historical fact were, first, Christianity, which neglected the body in favor of the soul, preferring to wait until the Day of Judgment to know about the body, and, second, the idea that the human body was a miniature universe and therefore it could be studied astrologically by looking at the heavens instead of at the body. That is why when anatomic studies began to make headway astrology declined.

ART AND MEDICINE

In order to comprehend the role played by Renaissance Art in the development of Medicine, we should remember that medical science and art have been closely related for long periods in History. In ancient civilizations, medicine, art, and religion formed an indissoluble trinity. The priest of primitive cultures was also the medicine man who, besides acting as an intermediary between gods and the people, used his influence with the deities to cure the sick. He was also the first patron of the arts, since he had to present the deities to his people in the most artistic form, which forced him to seek artists that would fashion the best images of the gods. Thus, the priest was not only a healer but a Maecenas.

In the Middle Ages, the trinity disintegrated and the medicine man and the artist became specialized figures, although art continued subserving religion. But in the Renaissance, art and medicine were united again. The need for representing the parts of the body with exactness forced the artist and the physician to become one and the same. But until dissections were authorized, the artist was forced to use diagrams of animals or make imaginary drawings of the human body.

A disease, because it is a dynamic process, can be fully described in words or, as it is done today, shown on a screen. Plastically, however, only one phase at a time in the course of the disease can be portrayed. This the Renaissance artist did when he painted the portrait of an important person who happened to be sick. He did realize, however, that anatomic structures could be better depicted with a brush or mallet than with words. The human body, a *terra incognita* that had to be explored along with new continents being discovered, began to yield its secrets to the artist, who had the advantage of a keen eye over the physician—*sapere vedere*, as Leonardo said.

The history of Anatomy changed the day an Italian artist, in order to carve a wooden crucifix for a church in Florence, obtained permission from the prior to remove the skin from a corpse and study its muscular anatomy.

ART IN THE RENAISSANCE

The historic period that stretched from the birth of Leonardo da Vinci to the death of Michelangelo is characterized by a return to Nature and the study of the human physical form. Florentine painting and sculpture, the most essential arts of the Renaissance, reveal a mystical softness and a sad vigor which reflect their medieval roots and the religious fanaticism of Savonarola and the popes. But it also reveals a pagan humanism that is a faithful image of the licentious court of the Medicis.

Renaissance art is turbulent and restless; it is the expression of a society continuously agitated by religious and civil strife and by the somber visions of the beyond which are still an integral part of the Florentine school. Enthusiasm over Nature and over man, as Nature's noblest manifestation, encouraged a methodical investigation of Nature through neo-Platonic philosophy. Moral life is reinvigorated, and the human mind turns back to the models of ancient art. In the social

order, manners are elegant but corrupt and violent. *Virtu*, that compound of despotism and cunning which Machiavelli advised the Prince to have as an indispensable quality, *onore*, described by Baltassare Castiglione in his *Cortesano*, religious fanaticism and excessive violence encouraged by the silence of public opinion, are determining factors in the shaping of Renaissance art.

Detail from Michelangelo's great fresco "Universal Judgment."

Reflecting this restless atmosphere, Florentine art leans to melancholy and languid grace as easily as to happiness or tormented painful realism. The major reason for this is Christianity which, primarily through the voice of Saint Francis of Assisi, defies pain, anathematizes the flesh, and adopts an attitude of mystic tenderness. Exuberant vitality and admirable anatomic precision are evident everywhere. Sculpture has a delicate firmness of line with a high level of tactile values; it represents a careful study of the morphology of man in repose or in action. Every line and color in painting throbs with life.

The contribution that Renaissance artists make to Medicine is more than just iconographic documentation or a series of static and dynamic morphologic observa-

tions; it is an awakening of interest in biologic man, a bending of studious minds to the observation of the form and functions of the human organism.

Disregarding symbolism and the mystical subtleties of medieval disquisitions, the artist aroused popular attention through his simple representation of Nature and of man in his complex and beautiful nudity. Thus, the human mind was directed towards science along the royal road of beauty.

Previous to the Renaissance, the artist created only stylized, almost imaginary, figures. But the Renaissance artist believed that the greatest beauty lay in a faithful copy of reality. In order to become acquainted with the human original, the artist studied details of external morphology as well as internal structures. Man became an object of physical study. A knowledge of man could be obtained, the artist realized, not by drawing away from him, as in the Middle Ages, not by depending on occult philosophies and astrology, but by closely observing the human being. Landscape became a backdrop. Michelangelo, dictator of this school, declared that the true object of art was man. With the decline of great art, landscape would be painted again, but it would still be only "a setting for pastorals and pomp" (Taine), a noble, measured accompaniment of "mythological gallantries and lordly outings."

This artistic interest in man had strong repercussions in Medicine. The physicians of the time were influenced by the artistic trend and, instead of studying man and his pathology through symbols and vague analogies, proceeded by deduction and the linking of facts substantiated by data gathered directly from man himself.

Italian painting in the Renaissance ceases to be mystical and theological, as it had been from Giotto to Fra Angelico, and becomes sensual and pagan. Paintings no longer depict the dreamy "Magdalenes," pensive virgins, and tragic martyrs of the old school of Bologna. The primary objective of painting is "to paint well a nude man or a nude woman," as Benvenuto Cellini stated. Artists use sculpture as their starting point, for they can palpate the muscles, curves, and bones. They wish to create a healthy, dynamic human body; theirs is the Greek ideal; athletic, caught in a fine plastic posture, as if telling God what He could have done with man if He had so desired.

Renaissance man experiences a strange dualism: to the dreams of the fanatic he joins the keen insight of the intellectual. Like the former, he thinks in images, and like the latter, he arranges them. Perfect physical forms are born and stylized in pictures.

THE PSYCHOLOGICAL MEANING OF RENAISSANCE ANATOMIC ART

What underlay the interest which the Renaissance artist took in the human body, in vigorous, dynamic figures?

The answer is based on a psychological fact. Art is escape. Art is flight from reality. The painter entrusts his most intimate feelings, desires, and anxieties to canvas. The "outer" art of a given period mirrors only the external appearances of that period, its *mise-en-scène*, its pretexts. But true painting reflects what did *not* happen at the time, the "unlived lives" of the artist—everything the reality of his times denied him.

The main trend of Greek art was to banish from statuary and painting all sensation of effort; but in doing so, they also eliminated inner life. The anatomic perfection of Greek statues hides an inexorable emptiness. Those polished marbles representing athletes with their muscles fully flexed cover up a *man in a state of mental repose*. Medieval art shows *man frightened* by the idea of life beyond death; it is an art of terrorized men who pooled their individual fears in a gigantic collective panic. To the Renaissance belongs *man on the defensive*, a mixture of saint, bourgeois, and adventurer endowed with intense inner vitality.

In order to understand the Renaissance artist's interest in the human body, an interest that ushered in a tremendous rebirth of anatomic studies and which, through Vesalius' efforts, would open the doors leading to modern science, we must recall the historico-social conditions of the period. It was an aggressive and cruel era, without peace or justice, during which exquisite manners covered up ferocious instincts. Machiavelli justified murder in his writings. Benvenuto Cellini, protected by Pope Paul III, boasted of his innumerable crimes in his *Life*, perhaps the best mirror of the times, and bragged about the blood his sensual indulgences had caused to flow in the streets of Rome. The Borgia Popes, members of a sensual and cruel Valentian family (Borja) that had settled in Rome, used terror as their principal weapon. The fear of death at the hands of tyrants or professional assassins tempered the Renaissance man and tautened his nerves. In this manner the times forged a biologic example of man on the defensive, fiery and restless, of ebullient intellect, impetuous in behaviour, with an imagination seething with sensual or religious images.

A way of life which requires that one must kill in order to stay alive naturally gives rise to an interest in the human body, in its muscles and its various dynamic postures; it tends to impress upon the memory all the attitudes of the body in action. Only men trained à la Cesare Borgia through all sorts of physical exercise could understand the body in painting or sculpture, because unconsciously they knew the importance of bones and muscles, of a flexed limb or a bent torso, of all the postures of the body at rest or in motion.

The lack of justice and the omnipresence of danger engendered great passions in Renaissance man, making him capable of enjoying paintings and statues depicting either strength and grandeur or innocence and simplicity. In keeping with the violent or somber states of mind prevalent at the time, people derived great pleasure from the sight of nude Madonnas or vigorous warriors. Out of involuntary sympathy, Renaissance man enjoyed gazing at the heroically bulging muscles of Michelangelo's figures, the health and softness of Raphael's Madonnas, the bold vitality of Donatello's bronzes, the strange beauty of da Vinci's creations, the animal sensuality and athletic joy of Titian's or Tintoretto's figures.

Benvenuto Cellini wrote enthusiastically of the "admirable bones of the head, the shoulder-blades which, when the arm is raised, produce magnificent effects, and the five floating ribs which, when the torso is bent back or forward, form marvelous projections about the navel." He also said, "You will draw the bone which is located between both thighs; it is very beautiful and is called the coccyx or sacrum.

. . . You will draw the vertebrae because they are magnificent." When Lucas Signorelli lost his beloved son, he removed all the clothing from the dead body and drew its muscles with great care. Pollaiuolo and Verocchio flayed dead bodies and committed to memory bones, muscles, and tendons, which they later copied in bronze or transferred to canvas. Thus, they were able to convey to the spectator the notion that beneath the skin there was depth, living flesh, and bones. This effect is evident in the six executioners of the "Saint Sebastian" of Pollaiuolo; their anatomies are displayed to the most minute detail. Another impressive study of muscles in action is the "Battle of the Ten Nude Men," by the same painter.

Artists fill the homes of noble Florentines with sensual, muscular nudes in which not a single bone or muscular defect of the model was overlooked—to have done so would have meant mutilating the individual.*

At the end of the fifteenth century, the study of dead bodies marks a return to Nature. The human figure represented on canvas ceases to be stiff and acquires life and dynamism. Broadsides on anatomy for students appear one century later in Bologna, Paris, Nurenberg, and Venice. Among them are the "Six Tables of Venice" printed by Bernardino Vitali and signed by a physician named Andreas Vesalius.

ANATOMY AMONG THE RENAISSANCE MASTERS. THE SCHOOLS OF FLORENCE, VENICE, UMBRIA: VEROCCHIO, BOTTICELLI, PIERO SIGNORELLI, DONATELLO, RAPHAEL, MICHELANGELO

Verocchio was one of the first Renaissance artists to revive anatomic exactness in painting. Ten years before his birth, John and Hubert Van Eyck had attempted the exact reproduction of figures on canvas. Masaccio, too, in his "Adam and Eve" depicted a middle class Florentine couple with all the imperfections of flabby nude flesh. But Verocchio represents a tremendous advance over his predecessors. In his "Virgin and Child with Two Angels," the Virgin is a simple woman with a serene countenance, long, slim fingers and well-delineated anatomy; the child is a healthy, chubby infant so well reproduced that his big toe shows the so-called Babinsky neurologic sign, normal in children of his age.

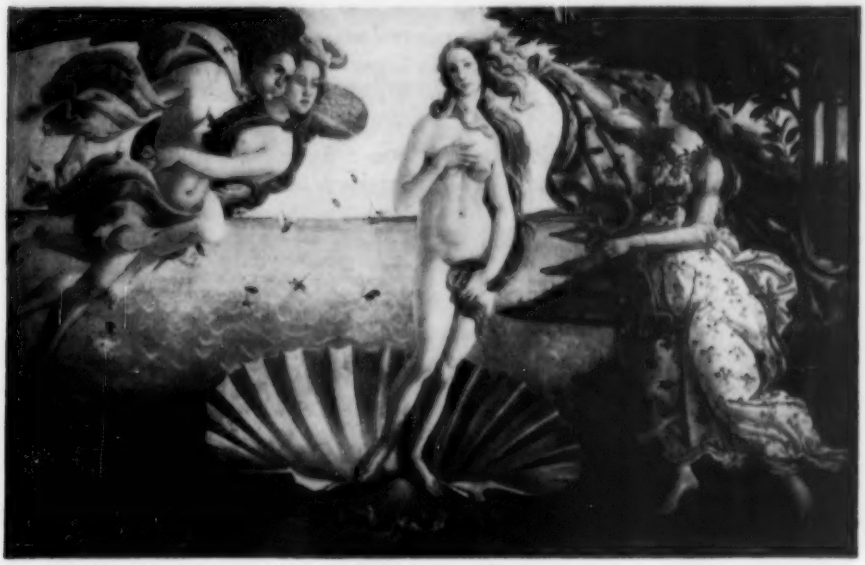
Somewhat younger than Verocchio was Sandro Botticelli, a disciple of Pollaiuolo

---

* The principles governing anatomic illustrations before the Renaissance were: (1) servile adherence to tradition and (2) observation of reality. The first made for diagrammatic anatomy which attempted to deduce nature from a structure of the function assigned to it by the Creator. The second made for artistic and morphologic anatomy, true living anatomy, the precursor of modern physiology.

In the fifteenth century, Florentine painters were already buying their pigments from the apothecary and thus had the opportunity of fraternizing with physicians. Artists like Masaccio entered the *League of Physicians and Apothecaries*. For two and a half centuries science and art constantly drew closer. Masolino, Roselli, Lucas Cranach, all apothecaries' apprentices, became great painters. Giotto had friendly relations with the physicians Dino del Garbo and Torrigiani; Luca della Robbia and Benivieni were friends, and so were Leonardo and Marco Antonio della Torre. Giotto wished to break with the flat dimension (in the fashion of the Byzantine mosaic) of his master Cimabue; he sought a tridimensional depth and solidity in the field of painting. The paintings of Stefano, his assistant, were studied by barber-surgeons before they opened the veins of their patients.

and of the Fra Filippo Lippi who painted chubby virgins and fat little angels. Botticelli was one of the most original of the Renaissance painters. Restless and unhappy, he translated his feelings into such exaggeratedly expressive lines that he induces a nervous vibration in the spectator. His paintings immortalized the tall, thin woman. The virgins of his "Primavera" are the quintessence of Florentine distinction, and their heavy abdomens reveal the painter's knowledge of the asthenic



"The Birth of Venus" by Botticelli, Uffizi Gallery, Florence, Italy.

habit, the *leit-motiv* of Botticelli's work.

Piero Signorelli was the Dante of fifteenth century painting. Impersonal and cold, he created stiff figures, tormented but stoic. However, the fierce emotions hidden beneath the stoic countenances can be sensed even in his virgins.

Florentine sculpture first boasts of a Donatello, whose statues of saints are characterized by a sharp naturalism and whose children ("David" or the "Angel with Timbrel") possess an exquisite grace. In his bronzes, Donatello has left us examples of robust anatomies, like his "Saint John" and "Anatomy of a Miser's Heart," and heads of sweet, sad virgins.

The second half of the fifteenth century witnesses the development of the Venetian school, deriving from the school of Padua and synthesizing Florentine elegance. It reflects the social life of the city, its people and their pastimes and rich attire, in a setting of luminous landscapes under skies of silvery clouds. The virgins of this school are beautiful young girls with golden hair, and the saints are happy youths attired in precious stuffs. Light, color, well-being, and cheer are the characteristics

of this art—characteristics that cannot be accounted for by the mild climate, but rather by that sort of moral and physical health usually associated with the opulent Flanders that Rubens painted. The red or golden hair and pink flesh stressed by the Venetian school derive most likely from the fact that these painters were especially sensitive to the chromatic impressions of red and yellow, colors usually associated with "primitive" men in full possession of their virile instincts. This school immortalized the type that Landouzy would later translate into medical language by the term "Venetian habit:" pink skin with blue veins, golden or red hair, and somatic frailty usually associated with tuberculosis. As verification, we need only recall the softly rounded virgins of Cima da Conegliano, the thin, nervous virgins of Crivelli, the dwarfs of Paolo Veronese, and the vital silver tones of Titian and Tintoretto.

The Umbrian school, characterized by poetic freshness, childlike grace, and translucent coloring, had its most brilliant exponent in Raphael Sanzio of Urbino, who died at the age of thirty-seven from overwork, tuberculosis, and his excesses with the lustful dancer la Fornarina.

Raphael was influenced by Timoteo Vitti and the French school; hence his fondness for round, opulent figures. For four years he was inspired by Perugino and Pinturiccio. He then went to Florence and there for another four years painted his immortal virgins, in imitation of Leonardo and Michelangelo. He became the favorite painter of Julius II and Leo X and decorated the loggias of the Vatican with half-mystical, half-pagan virgins. In his unfinished "The Transfiguration," he made some magnificent contributions to anatomy, such as the relief of the muscles, the lumbar slope, and the flexed back of a young woman kneeling.

Raphael's anatomic exactness may be ascribed to the years he spent in Perugino's studio studying the forms of mystical figures or of sweet Madonnas. With these impressions and his earlier memories, he forged an ideal of strength, youth, and cheer. Raphael succeeded in thinking in terms of form and translated all his aspirations into contours and postures. It is no wonder that at the age of twenty-five he was the outstanding painter of his time.

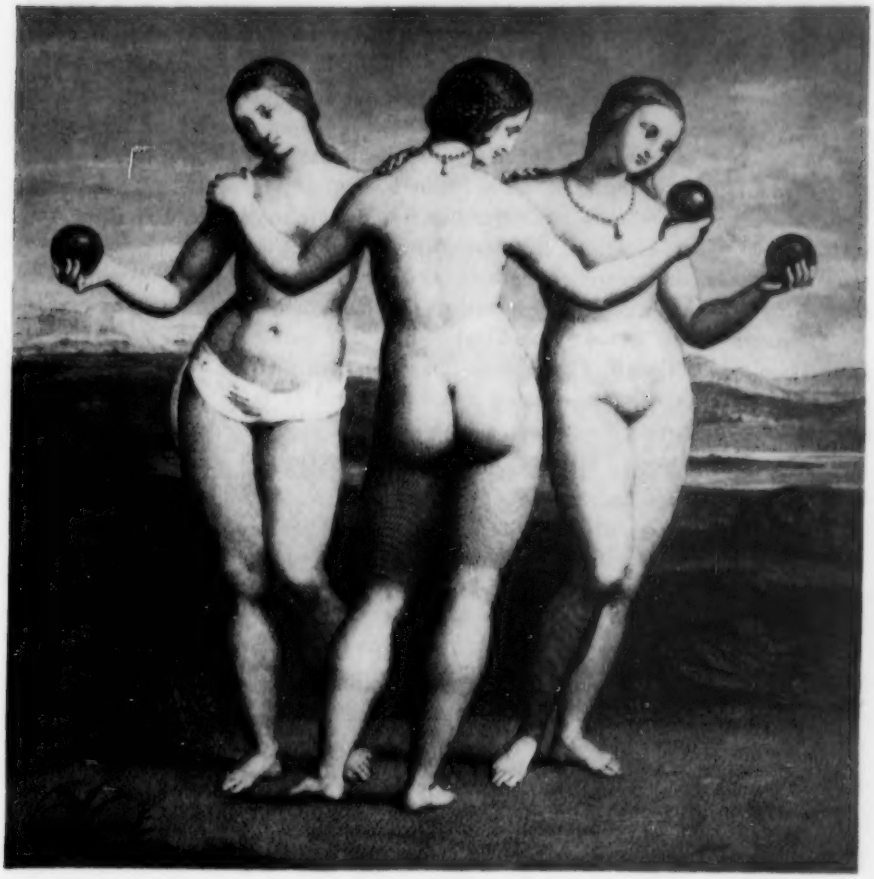
Raphael made some admirable medical observations in his "Saint Peter and the Lame Man" and in "Tomasso Inhinami" in which he depicted divergent strabism. His portrayal of the timid virgin in the "Madonna di Faligno" is a psychological study and reveals great mastery of anatomy, particularly in the child, whose soft thigh shows an inguinal fold which was doubtlessly significant to the artist. Raphael loved the contour of a vigorous naked thigh and the vitality of a muscular back. His "Descent from the Cross" is a hymn of praise to the adolescent body; his "Graces" are heavy, fleshy girls, and the cupids of his "Psyche" have the pink, thick-textured flesh of well-nourished children.

But plasticity, strength, and dynamism of the living body reach their apogee with the Florentine, Michelangelo Buonarrotti. Michelangelo was a poet, architect (he built the Basilica of Saint Peter), painter, and, above all, sculptor. "I, Michelangelo, sculptor," was the signature on his letters.

From early youth, Michelangelo worshipped beauty of form. Dante Alighieri's

immortal poem and Savonarola's fiery sermons forged the temperament of that Michelangelo whose greatest urge was to impose his genius on marble and canvas. Only man interested him; and the men he created were giants, their gestures eloquent, their sharp postures tormented, their muscles tense to the point of almost overflowing the limits of possibility. His virgins are fiercely naked, and his captives arch their backs with formidable strength. Michelangelo played on the human body as on a musical instrument from which he extracted brilliant, grave, strident sounds. He created a school of gigantism that became artificial and mannered in the hands of his successors.

In order to acquire a sense of reality, Michelangelo used live models. With the permission of the prior of the Monastery of Santo Spirito, who assigned him a cell for the purpose, he dissected dead bodies which he secured from the grave diggers



"The Three Graces" by Raphael.

of Florence in exchange for statuettes he had made. In his improvised bare studio, he would insert a candle in the navel of the corpse and tirelessly study the muscles, tendons, and ligaments, the same muscles, tendons and ligaments that stand out so fiercely under the polished marble of his "Solitude" or his "Moses."

Thus, Michelangelo became acquainted with the mechanism of human dynamics and the structures of bones and muscles; he familiarized himself with all the postures of the human body and learned how to make them portray the hidden torments of the soul. His "David" is a masterpiece of anatomy; in his "Virgin and Child" one can almost see the trembling of the Madonna's fingers, and his "Florentine Soldiers Bathing in the Arno and Surprised by Pisans" is an anatomic wonder.

Michelangelo lived alone. He was a chaste giant, without any love other than what he felt for Vittoria Colonna, the wife of Pescara. His figures bear the impress of his soul; they are somber creatures, athletic and dreamy, showing (such was his mastery of musculature!) anger or fear even in an inguinal fold or in the relief of a shoulder blade.

Before decorating the ceiling of the Sistine Chapel for Julius II, a work which occupied him for four years, Michelangelo sought inspiration by reading Dante among mausoleums. The Sistine Chapel displays tremendous figures, radiant with the strength of flexed muscles, beings who belong to a superhuman race. His "Moses" (the statue which adorns the Church of San Pietro da Vincoli in Rome and which Freud psychoanalyzed) overflows with "repressed emotion," passion, and anger. There is even greater strength in his four statues lying on sarcophagi, with their exhuberant and exasperated musculature. But all the possibilities of motion are exhausted in his fresco "The Final Judgment," painted at the command of Paul III on the back wall of the Sistine Chapel and which took him seven years to complete. In that work he created a sinister world of nude angry giants with prodigious musculature; the herculean Jesus gives the impression of a feverish Titan bordering on madness. This work alone, "an apotheosis of nudity," symbolizes the Renaissance.

AND—LEONARDO

Leonardo da Vinci personified all of Renaissance culture, all dreams of progress and glory, and all love of beauty and science.

The author has already written the story of Leonardo's life and the romantic legend which grew up about him.* Although Leonardo's wanderings were limited to only three places—Florence, Milan, and Amboise-sur-Loire—his intellectual range was universal. Leonardo the scientist is an encyclopedia of things to come. But here we are interested only in Leonardo the anatomist.

Leonardo underwent his artistic apprenticeship in Verocchio's studio, where he

* Martí-Ibáñez, F.: Leonardo da Vinci, Universidad de Madrid (Spain), 1934, and The Lives of Leonardo, Town and Country, *106*:55 (December) 1952.

spent innumerable hours dissecting dead bodies and developed a strong liking for anatomy as a vehicle for beauty. Later he performed dissections at the Hospital of Santa Maria la Nuova. In his own studio he worked on clay figures which he later painted, imitating relief with his brush and thus introducing into painting the sensation of solidity. Even his first work, "The Adoration of the Magi," is a miracle of anatomy.

Drawing of Leonardo by himself.

Leonardo's personality has not yet received the thorough study it deserves. Unfortunately, the artist has eclipsed the scientist, and interest in the picturesque artistic atmosphere in which he moved has drawn attention from his scientific accomplishments. The 500th anniversary of his birth brought to light new facets of his genius and confirmed him as perhaps the most extraordinary being that ever existed. Others, like Goethe, may have possessed as vast a knowledge and may even have surpassed him in their ability to integrate harmoniously all the facets of their lives, but nobody has ever matched the dazzling flame of genius that burned in him.

In the six thousand odd closely written pages of his diary, studded with brilliant illustrations, we find the seed of our modern science. Recently, English and American medical journals have published a series of studies on Leonardo's work in the various fields of anatomy, physiology, and medicine. The outstanding anatomists, physiologists, cardiologists, geriatricians, and ophthalmologists of today are amazed to discover that Leonardo knew the basic principles of their specialties, and in many cases they find his views to be identical with those held today. The anatomic studies that he started in 1472 were not published until modern investigators uncovered them. Had they been made public in Leonardo's time, the circulation of the blood might conceivably have been discovered in the sixteenth century instead of in the seventeenth. The loss the scientific world suffered at the disappearance for several centuries of Leonardo's amazing scientific work can only be matched by the loss to the artistic world of his equally amazing anatomic illustrations. One of these illustrations, lent by the Queen of England to the centenary exhibit, shows a fetus in the womb with an incredibly expressive face. The child's face seems illuminated by a prophetic vision of imminent life and its drama. It is perhaps the most beautiful anatomic figure ever created.[1]

Leonardo's achievements in anatomy are only a small part of his prodigious work,

One of the hundreds of anatomical studies made by Leonardo.

which included engineering, mechanics, and science in general. He completed nothing that he started, spread himself too thin, changed his direction too often, and his work was almost completely unknown until the last century. His methods were still being discussed by painters when, thirteen years after Leonardo's death, Vesalius came to Italy and found his compatriot van Kalkar still imbued with Leonardo's influence. Between them, they reconstructed a part of Leonardo's spirit in the field of scientific anatomy.

Leonardo, who accepted Galenism but advanced the notion of the circulation of the blood which Harvey would later discover, adequately described the position of the liver, spleen, and kidneys. In his drawings he anticipated by one century the discovery of Highmore's maxillary sinus. His studies of the influence of age on the organs, deriving from his dissection of corpses of old men, are the forerunners of contemporary geriatric research; his studies of the human eye are likewise notable.

Refuting Galenic ideas which had been accepted for 1200 years, Leonardo demonstrated that the heart was a muscle and described two new cavities—the auricles—which he added to the two ventricles Galen had described.

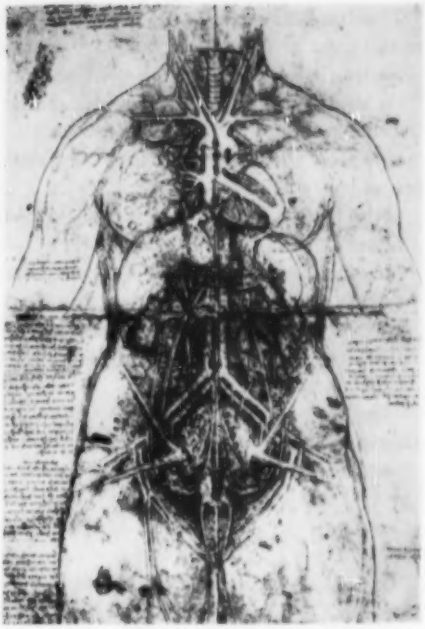
Leonardo's "Diary" contains 190 pages devoted to anatomy, of which 50 are about the heart. His approach to anatomy was that of an artist who, although guided by Galenic ideas, formulated mechanical laws to replace supernatural principles and the ancient analogy between the macrocosm and the microcosm. For example, while watching the farmers of Tuscany slaughter their pigs by driving a *spilla* or long pin into the heart, he observed the contraction and dilatation marked by the pin and thus discovered the cardiac sistole and diastole.

Leonardo dissected more than thirty corpses and planned to write a 120 volume treatise on anatomy.* His drawings supersede Galen and restore the anatomic

* In October, 1517, Cardinal Luis of Aragon and his Secretary paid a visit to Leonardo da Vinci at his home in Amboise. The Secretary notes of the visit: "This gentleman has written of anatomy with such detail showing by illustration the limbs, muscles, nerves, veins, ligaments, intestines, and whatsoever else there is to discuss in the bodies of men and women, in a way that has never yet been done by anyone else. All this we have seen with our own eyes; and he said that he had dissected more than thirty bodies both of men and women of all ages. He has also written of the nature of water, of diverse machines and of other matters which he has set down in an infinite number of volumes all in the vulgar tongue, which if they should be published will be profitable and very enjoyable."

dignity of man. He studied the fetal membranes and denied that the fetus can cry in the uterus. He described bone textures and muscular functions and placed bones in wire boxes to study their dynamics. Fascinated by mechanical laws, he studied muscular antagonisms and correctly ascertained the points of insertion and outlet of a muscle. He injected the cerebral ventricles with liquid wax and also described the pleura and lungs, but did not emphasize the circulation of the blood, since to have done so would have been heretical. With such work, he created the experimental method.*

As a painter, Leonardo represents the culmination of the realistic trend started by Andrea da Castagno. His theory of painting is summarized in the advice he gave his disciple Giovanni Beltraffio: "The painter's soul should be like a mirror: it should reflect movement and color while it itself remains motionless, limpid and pure."



A detailed study of the internal organs by Leonardo (from the collection at Windsor Castle)

Leonardo believed that a scientific knowledge of artistic anatomy, quite different from the intuitive knowledge of static or dynamic nude figures which the Greek sculptors created, could be acquired only on the dissecting table. Many times his cold blue eyes bored into the dead human body while his delicate, almost feminine, hands felt out anatomical structures, measured longitudes with goniometers, figured out proportions, and reduced parts of the organism to mathematical formulas.

He studied people and their expressions in various states of excitement, but he made sure they did not perceive what he was doing so that they would not become self-conscious. "Study the expressive movements of deaf-mutes," he counselled. He was obsessed by the desire to translate states of mind somatically onto canvas.

---

* Thus spoke Leonardo: "And you who say that it is better to look at an anatomical demonstration than to see these drawings, you would be right if it were possible to observe all the details shown in these drawings in a single figure, in which with all your ability you will not see, nor acquire a knowledge of more than a few veins. While in order to obtain an exact and complete knowledge of these I have dissected more than ten human bodies, destroying all the various members, and removing even the smallest particles of flesh which surround these veins. . . . And as one body did not suffice for so long a time, it was necessary to proceed by stages with so many bodies as would render my knowledge complete; and this I repeated twice over in order to discover the differences.

"Though possessed of an interest in the subject you may perhaps be deterred by natural repugnance . . . or fear of passing the night hours in the company of these corpses quartered and flayed and horrible to behold."

"Diversity of movement is as infinite as diversity of feeling," he said. "The loftiest aim of the artist is to express the passions of the soul on faces and in movements." Painting was his religion: "*Chi biassima la pittura biassima la Natura.*" His painting is a blend of perfect figuration and precise chiaroscuro. His anatomically impeccable figures combine a singular gelatinous softness, personified in Mona Lisa's mollusk smile, and a disturbing lack of consistency; each method is used to translate a state of mind.

His "Last Supper," painted in oil on the wall of the refectory of the Monastery of Santa Maria delle Grazzie, is a miracle of psychological observation. Today it is blackened and mutilated by a door which the Renaissance monks cut through the wall so their food would not arrive cold from the kitchen. His painting of Mona Lisa, the Gioconda, third wife of the Florentine Francesco del Giocondo, took him four years, and to make the lady smile he surrounded her with all sorts of pleasant objects and even provided music.*

Leonardo's chalk drawings laid the foundations for artistic anatomic iconography. Buried in oblivion for two hundred years, these drawings, copies of which may be found in the work of Dürer and in the Uffizi skeletons in Florence, are surrounded by marginal notes of great exactness, written from right to left—which Leonardo found easy to do since he was left-handed—out of fear of plagiarism or the Holy Office.

In all, Leonardo made more than 750 drawings of muscles, the heart, lungs, the cervical, thoracic, abdominal and femoral blood vessels, bones and nerves after performing minute visceral dissections and sagittal and frontal cuts of the brain.

Among his curious physiological observations are those he made of facial muscles in laughter and tears. His desire for exactness led him to study dispassionately the facial anguish of men condemned to death, engraving their slightest gestures during execution on his brain for future use. To be able to recall these faces, he thought of a method, which anticipated the Bertillon system now used in legal medicine, based on a division of noses into straight and curved, the straight into short and long with round or pointed extremities, and the curved noses into three groups according to the curvature. These divisions and sub-divisions were given numbers; all he had to do, therefore, to be able to recall a face later on was to jot down the numbers that stood for the characteristics of the nose, mouth, and eyes. He also worked out a gradation of the colors of the rainbow. His collection contains

---

* The "Mona Lisa" may have been the image of his mother, since it is possible that Leonardo was a timid type because of superdifferentiation of instinct. He sought an inaccessible ideal and fled from women out of a need for absolute calm and liberty to work. It is said that he loved only once in his life and even in that case it was by way of a scientific experiment; all his life, however, he evinced his aversion for the sexual act. "He who does not control his sensuality lowers himself to the level of the beast," he said. "The carnal act and the organs it involves are so coarse that if it were not for the beauty of the faces and adornments of human beings, and the unbridled impetus which carries them away, mankind would go lost." "Mona Lisa" may be the portrait of the artist's most cherished ideals, for her smile is perpetuated in all of Leonardo's works, especially in "Saint Anne" and "Leda." Leonardo and Mona Lisa are two mirrors reflecting the same image. The outer aspect of "Mona Lisa" conceals a portrait of Leonardo himself, for when he looked upon his model, La Gioconda, he felt that the entire physical being of that woman lay hidden in himself.

many drawings of monsters and abnormal beings, dropsy victims and goiterous old men of the Bergamasc mountains, strange animals, porcupines, cats, fish, flies and birds.*

Leonardo's accomplishments in medicine were prompted by his desire to achieve the greatest possible knowledge of anatomy to help him in his art and by his desire to know *per se*, which inspired his frenetic search for the scientific truth.

His medical studies established an anatomic canon based on a "natural" ideal, in opposition to the canon based on a "divine" or unattainable ideal. Leonardo called himself "*il pittore anatomico*" but never allowed anatomy to impinge upon his artistic genius; he urged painters not to try to show the entire play of the muscles in their nudes.

Bettman Archive
Study of the human form (woodcut) by Vesalius.

Leonardo was the first to approach science as an artist and to use the scientific study of Nature as a vehicle that would lead him to supreme mastery of the artistic sketch. It was not enough for him to reduce natural laws to mathematical formulas; he had to go further and dramatize them in drawings. In this sense, his work was a crusade against the esoterism which had enveloped science before his time. His great desire was to show man's knowledge encyclopedically. It is possible that had Leonardo not exhausted himself in so many directions and had he systematized his work, it might have embraced the following fields: Mathematics and Optics as the basis of all observation; Mechanics as the science of all physical—organic and inorganic—forces; Biology as the science of life and growth in organic nature; and Cosmology as the study of inorganic forms.

---

* Leonardo invented a many-stringed lute of silver in the form of a horse's head which Ludovico il Moro greatly admired; Leonardo took advantage of this opportunity to offer himself to Ludovico as an inventor of instruments of war, builder of movable bridges and tanks, an engineer, an expert in artillery and the art of sieges, a sapper, astronomer, sculptor, and painter. It was at Ludovico's court that Leonardo showed himself to be a polemicist in Paleontology and Geology by outlining the scientific bases of Prehistory. He worked seventeen years on an equestrian statue of Ludovico's father, Francesco Sforza, and in his polyfacetism he showed himself to be the refined inventor of all modern ideas and the precursor of all modern advances. After carefully observing the flight of birds, he constructed a batlike flying machine heavier than air. He did not, however, succeed in his ambition of enabling man to fly, and he put his machine away in a corner of his studio along with his dissected crocodiles and embryos in alcohol. He was also a chemist, geologist, and a researcher in camera obscura.

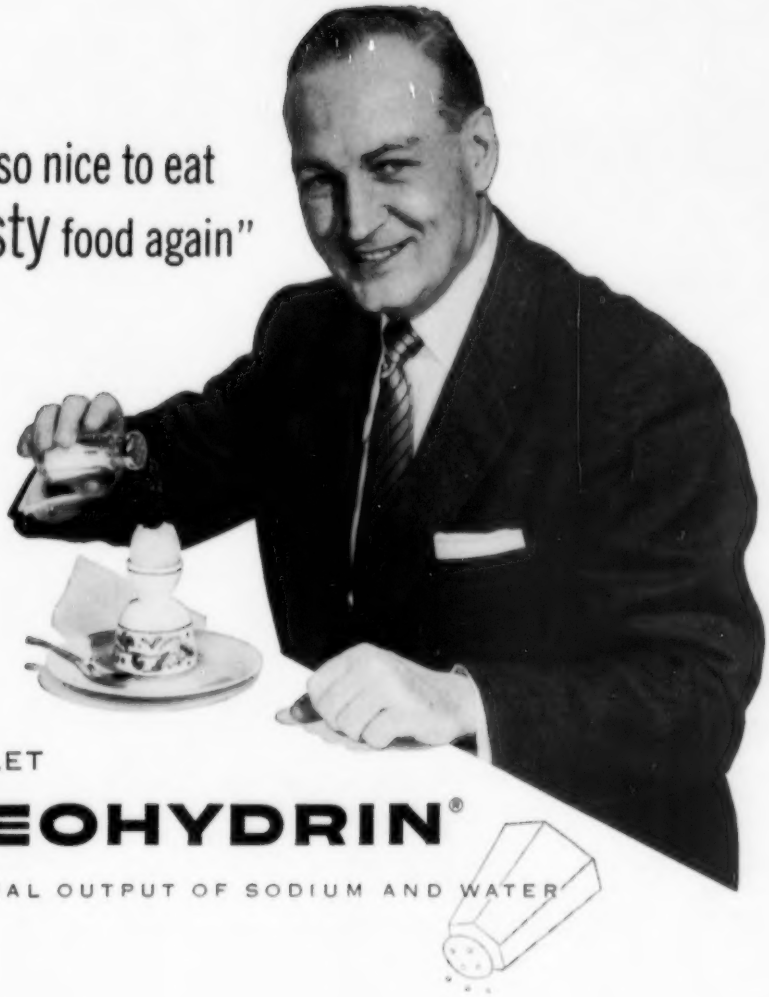
To the religious fanatics of his time, Leonardo was a skeptic. It is said that during a fiery sermon delivered by Savonarola to a horde of people cringing at his feet, Leonardo, his corpulent figure erect under a black and red tunic stood nearby, listening impassibly to the preacher's apocalyptic prophecies. And as he listened he scornfully drew a caricature of the tormented priest.*

Leonardo da Vinci, poet, man of letters, musician, sculptor, physicist, painter, architect, engineer, geologist, anatomist, psychologist, alchemist, naturalist, anthropologist, philosopher, and constructor of flying machines and tanks, is the most amazing personality of the Renaissance. His was the mind of the Renaissance, ever eager to fly off to new horizons. His contribution to Modern Medical Science began to take shape when, thirteen years after his death, there arrived in Italy a Belgian anatomist with a restless mind and a firm hand. This man was Vesalius. With the advent of Vesalius, the physician would become an artist *and* a scientist.

* Leonardo was neither an atheist nor a devotee of black magic. His was a universal religion, for he worshipped the divinity in flowers, insects, and the stars. He would not eat meat because he believed that animals had souls and should not be slaughtered. "The carnivorous man, in his cruelty," he said, "is *re delle bestie*." His enthusiasm for Nature led him to scorn physicians, whom he called "liars and destroyers of life." He had the opportunity of dramatizing this scorn for doctors in the case of the death of Dux Jean Galeas and during the illness of his pupil Andrea Galaino, when he threw the pills prescribed by their doctors out of the window.

His imagination was so vivid that he could see figures in the stains made by dampness on the walls and could hear voices in the ringing of far-away bells. Everything stirred him to psychological observation which he recorded with his left hand (he was naturally left-handed) and from right to left, in the Oriental fashion.

"it's so nice to eat
tasty food again"



TABLET

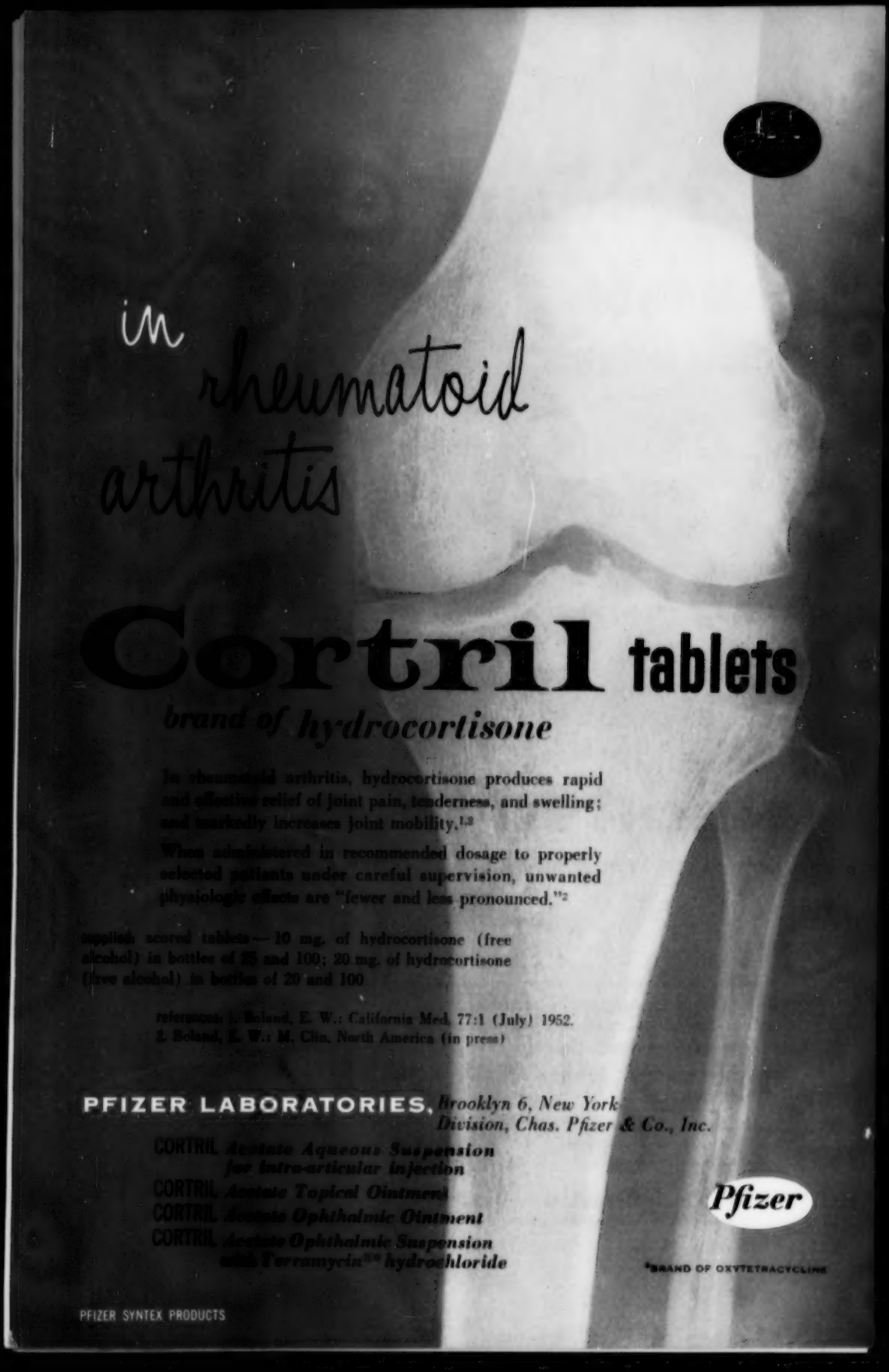
NEOHYDRIN®

NORMAL OUTPUT OF SODIUM AND WATER

PRESCRIBE NEOHYDRIN whenever there is retention of sodium and water except in acute nephritis and in intractable oliguric states. You can balance the output of salt and water against a more physiologic intake by individualizing dosage. From one to six tablets a day, as needed.

PRESCRIBE NEOHYDRIN in bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

Leadership in diuretic research
Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN


in rheumatoid arthritis
Cortril tablets
brand of hydrocortisone
In rheumatoid arthritis, hydrocortisone produces rapid and effective relief of joint pain, tenderness, and swelling; and markedly increases joint mobility.[1,2]
When administered in recommended dosage to properly selected patients under careful supervision, unwanted physiologic effects are "fewer and less pronounced."[2]
supplied: scored tablets — 10 mg. of hydrocortisone (free alcohol) in bottles of 25 and 100; 20 mg. of hydrocortisone (free alcohol) in bottles of 20 and 100
references: 1. Boland, E. W.: California Med. 77:1 (July) 1952.
2. Boland, E. W.: M. Clin. North America (in press)
PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.
CORTRIL Acetate Aqueous Suspension for intra-articular injection
CORTRIL Acetate Topical Ointment
CORTRIL Acetate Ophthalmic Ointment
CORTRIL Acetate Ophthalmic Suspension with Terramycin* hydrochloride
Pfizer
*BRAND OF OXYTETRACYCLINE
PFIZER SYNTEX PRODUCTS